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SURGICAL THERAPY OF TEMPORAL LOBE SEIZURES

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MONTREAL, CANADA

DURING recent years the mechanisms involved in the production of focal temporal lobe seizures have gradually come to light. Many cases of epilepsy, formerly considered idiopathic, are now to be recognized as focal cerebral attacks. The result is that new knowledge has been gained of the function of the human temporal cortex and a new field of surgical therapy presents itself.

In this paper we shall content ourselves with an analysis of the results of surgical therapy. In all of this work we have been greatly helped by Dr. Herbert Jasper; indeed, some of our success would have been impossible without his collaboration.

This analysis covers a 10 year period which ended in April 1949. During that time 68 patients who suffered from temporal lobe seizures were operated on.[1] The fact that during the 12 months that have followed that period 30 more such patients were subjected to operation illustrates how rapidly this field is expanding.

GENERAL OBSERVATIONS

It has long been recognized (Bravais,[1a] 1827) that epileptic seizures may be associated with abnormality of the motor area of the cerebral cortex; and it is an old story that localized discharge in various parts of the cortex may produce local fits, which may, in turn, lead to generalized convulsion (Jackson,[2] 1870).

From the Department of Neurology and Neurosurgery, McGill University, and the Montreal Neurological Institute.

Read at the Seventy-Fifth Annual Meeting of the American Neurological Association, Atlantic City, N. J., June 14, 1950.

1. The operations were carried out by one of us (W. P.) and occasionally by one of our associates in Montreal, Dr. Theodore Rasmussen or Dr. Keasley Welch. The follow-up analysis was carried out by the second author (H. F.).

1a. Bravais, L. F.: Récherches sur les symptômes et le traitement de l'épilepsie hémiplégique, Thesis, Faculty of Medicine, Paris, 1827.

2. Taylor, James, and others: The Selected Writings of John Hughlings Jackson, London, Hodder & Stoughton, 1931-1932.

Our problem today is that which was outlined for us by Hughlings Jackson—to discover in each case the location of the origin of the discharge. It is possible to do this in a rapidly increasing proportion of cases of cerebral seizures.

In essential, or idiopathic, epilepsy it is now apparent that the discharge originates in a centrally placed zone of gray matter in the diencephalon, midbrain and pons which is connected with both cerebral hemispheres. This gray matter we may refer to as the central integrating system of the higher brain stem. It seems to be the site of Jackson's "highest level." Attacks which begin there produce unconsciousness from the beginning. These are highest level seizures, and the electroencephalogram is often pathognomonic for this type. It demonstrates bilaterally synchronous 3 per second spike and slow wave complexes (Gibbs, Davis and Lennox,[3] 1935).

On the other hand, discharge which occurs in the cerebral cortex may produce a wide variety of symptoms or signs, depending on the function of the area in question. This may be movement or sensation. It may also be a change in thinking, a memory or a dream.

If an electrode can be placed near the site of discharge, the electrograph records discharges of electrical potential so brief that the recording ink writer makes a series of "spikes" on the moving paper. If the focus is buried deep beneath the temporal lobe, for example, electrodes on the scalp may fail to detect the spike discharges, but the electroencephalographer may report bilaterally synchronous alterations of brain waves that have been set up because, apparently, the spike focus under the temporal lobe is firing into a rhythmic mechanism within the higher brain stem. This "paroxysmal dysrhythmia" may take the form which Gibbs, Gibbs and Lennox [4] described as "psychomotor," as pointed out by Jasper [5] and Jasper and Kershman.[6]

TEMPORAL GRAY MATTER

If the cortex of the temporal lobe could be unrolled to form a map, as in the accompanying figure, it would be apparent how large this mantle of gray matter is. Results of stimulation suggest that the gangli-

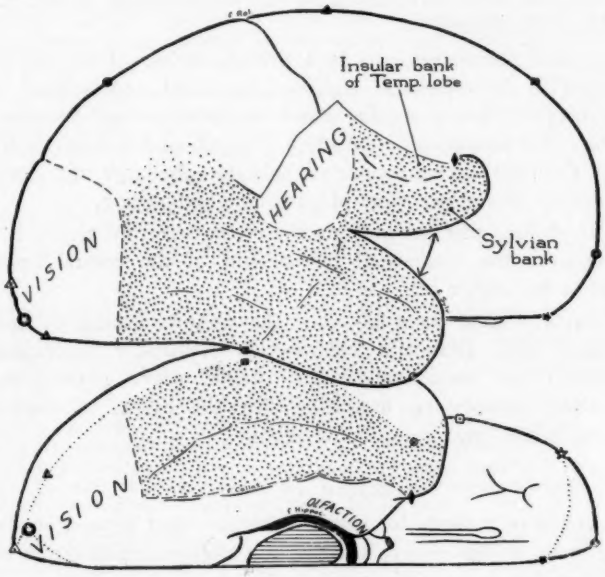
3. Gibbs, F. A.; Davis, H., and Lennox, W. G.: The Electro-Encephalogram in Epilepsy and in Conditions of Impaired Consciousness, Arch. Neurol. & Psychiat. **34**:1133-1148 (Dec.) 1935.

4. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: Cerebral Dysrhythmias of Epilepsy: Measures for Their Control, Arch. Neurol. & Psychiat. **39**:298-314 (Feb.) 1938.

5. Jasper, H. H.: Electroencephalography, in Penfield, W., and Erickson, T.: Epilepsy and Cerebral Localization, Charles C Thomas, Publisher, Springfield, Ill., 1941, chap. 14.

6. Jasper, H., and Kershman, J.: Electroencephalographic Classification of the Epilepsies, Arch. Neurol. & Psychiat. **45**:903-943 (June) 1941.

onic patterns which form the anatomic basis of memory are situated within the stippled portion of this gray matter, especially that on the superior and lateral surfaces of the lobe. The temporal cortex is bordered by visual cortex posteriorly. On its sylvian surfaces are found the auditory and vestibular areas, and, deep in the sylvian fissure, it borders the insula, which seems to be related to alimentary function. On the under surface of the lobe is situated the olfactory cortex of the uncus, the amygdaloid nucleus and the hippocampus.



Map of the temporal cortex. The superior surface of the lobe, which is buried within the sylvian fissure, has been turned upward. In the dotted portion of the temporal cortex are to be found ganglionic patterns which form the anatomic basis of memory.

Within this great cortical sheet there is, of course, an area that is devoted to memory of the spoken and written word; this is located in the posterior temporal cortex of the dominant hemisphere.

The results of stimulation and the effect of epileptic discharge show that there must be a great variety of representation of function in all these structures. This includes the function of the alimentary system and the mechanisms of dreaming, remembering and interpretation of the meaning of present experience.

FOCAL TEMPORAL LOBE SEIZURE

Attacks which arise in the temporal fossa are usually ushered in by characteristic initial phenomena. The commonest temporal aura is a sensation in the abdomen, epigastrium, thorax or throat. Cephalic auras and auditory, labyrinthine and olfactory auras are frequent. Illusions of perception may occur, such as the sudden appearance of a sense of familiarity or strangeness in the present environment, fear or a sense of greater distance or greater proximity of things seen or heard. Psychical hallucinations may occur like dreams, during which the patient may continue to be conscious of his real surroundings, as well as of his dreamlike experience.

All these phenomena may be a prelude to loss of consciousness or alteration in consciousness without convulsion and without loss of motor control. These are the states of confusion and amnesia which may be called behavioral automatism or psychomotor state. Such states appear during the continuance of epileptic discharge and during the immediately succeeding stage of ganglionic exhaustion.

It is obvious that the gray matter of the temporal region is closely connected to the intellectual mechanisms of the central integrating system in the higher brain stem.

From a clinical point of view, the unconsciousness or confusion associated with automatic behavior is frequently associated with mastication and swallowing. The patient never remembers these masticatory movements, indicating that the origin of discharge is temporal in the great majority of cases.

SELECTION OF PATIENTS

Selection of patients for surgical therapy must depend on discriminating study of the seizure pattern, the electroencephalogram and the pneumographic and roentgenologic evidence.

It has been our invariable rule that before operation all patients should have had well supervised medical therapy with maximum doses of diphenylhydantoin (dilantin®) or phenobarbital, and often other drugs. After operation, these patients have been given nothing but phenobarbital; and when the result seemed satisfactory the dose of this drug has been reduced progressively, so that each patient who does well usually discontinues anticonvulsant medication in one to three years.

MATERIAL

We have collected all cases in which operation was performed for temporal lobe epilepsy in the Montreal Neurological Institute during the 10 year period from Jan. 1, 1939 to April 1, 1949. Thus, there has been a postoperative period of one to 10 years for follow-up assessment of success or failure.

The series is made up of 68 cases, as shown in table 1. In seven cases exploration only was carried out. The origin of the seizures could not be recognized in these cases, so that no excision was attempted. None of the 7 patients was relieved of his attacks. One patient died after operation.

There were five cases of infiltrating tumor which had given no preoperative evidence of increase of intracranial pressure. The tumors were, of course, removed. In 55 cases an atrophic or stationary epileptogenic lesion of the cortex was excised. Included with these stationary lesions were three hemangiomas.

Seven patients had two operations, so that there were 68 patients and 75 operations with one death, an operative mortality of 1.3 per cent and a case mortality of 1.5 per cent.

TABLE 1.—*Operations on the Temporal Lobe (January 1939-April 1949)*

	Cases	Operations
Neoplasms without preoperative pressure signs	5	5
Atrophic or stationary lesions excised	55	62
Surgical explorations without excision	7	7
Postoperative death (hemorrhage)	1	1
Total no. of cases (mortality, 1.5%)	68	..
Total no. of operations (mortality, 1.3%)	..	75

NEOPLASMS

Eight patients were found to have neoplasms as the cause of seizures, although the diagnosis on admission had been focal cerebral seizures. These tumors, exclusive of the hemangiomas, were classified as follows:

	Postoperative Time	*Result (group)*	
Case 1 Astrocytoma	16 mo.	Recurrence, death	(0)
Case 2 Astrocytoma	2 yr.	No attacks	(4)
Case 3 Ependymoma	2 yr., 3 mo.	One attack	(3)
Case 4 Cholesteatoma	2 yr.	Decrease in frequency	(1)
Case 5 Cholesteatoma	Accidental death in first year		

The preoperative duration of seizures in these cases of neoplasm was 32 years, 3 years and 1 year for the gliomas; 5 years and 2 years for the cholesteatomas, and 8 years, 2 years and 1 year for the hemangiomas. As the hemangiomas showed little or no evidence of expansion, the cases are analyzed in the next section.

CLASSIFICATION OF RESULTS OF EXCISION

This follow-up study is concerned with the 55 cases in which the epileptogenic focus was apparently identified and a larger or smaller part of the temporal lobe excised. Fifty-one patients have been followed up to the present time, a period of one to 11 years after operation. The method of scoring results is similar to that employed by Penfield and Steelman [7] in their report of 59 cases of cortical excision in various areas of the brain.

7. Penfield, W., and Steelman, H.: The Treatment of Focal Epilepsy by Cortical Excision, Ann. Surg. **126**:740-762, 1947.

The results are tabulated under group headings 4, 3, 2, 1 and 0.

Group 4: In this group are included patients who have had no attacks after leaving the hospital and who consider themselves cured.

Group 3: The patients in this group also consider themselves cured, but they have had at least one attack since operation. Many have passed the subsequent years without an attack. None has had more than two attacks in any year. We do not place patients in this group unless we consider the result satisfactory.

Group 2: The patients consider themselves at least 50 per cent improved. Many included in this group place the improvement much higher.

Group 1: The patients consider themselves 25 per cent improved.

Group 0: The patients consider that there has been no improvement as the result of operation, or that their seizures are more frequent since operation.

TABLE 2.—*Results of Fourteen Excisions of the Temporal Lobe (1939-1944)*

Groups		Cases		
0	No improvement	1*	14% Failure	
1	Slight improvement	1†		
2	"Improved 50%" or more	4	29% Results worth while	
3	"Cured," with one or more attacks before cessation	3	57% Success	
4	"Cured," with no attacks	5		

* Further operation successful.
† Further operation proposed.

In all the foregoing classifications the patient's own estimate of improvement is not accepted unless it is borne out by other evidence.

ATROPHIC LESIONS

The results of operation in the 55 cases of excision and the seven cases of exploration with negative results may now be examined. Fifty-one patients in the former group have been followed to date. An atrophic lesion was recognized in all but three of the cases of excision.

Table 2 shows the results of operation. It is seen that 14 of the 51 excisions have been followed by a perfect result of no attacks. Thirteen patients were dropped to classification in group 3 because they had one attack, early or late, after operation, or they had a few attacks, after which the seizures disappeared. All patients in this group consider themselves "cured." If these two groups are combined, the results may be graded as successful in 52.9 per cent. All these patients either are taking no medicine or are receiving small amounts of phenobarbital.

Of the 13 patients in group 2, all consider themselves "50 per cent improved" by operation, and some considerably more. Many of the

patients in the lower groups are again using various forms of medication, as they were doing before operation.

By contrast, the results in the group of seven cases of exploratory craniotomy without excision are quite different from those in the foregoing groups. A diagnosis of epileptogenic lesion of the temporal lobe had been made, but excision was not deemed wise because of fear of aphasia or because a lesion or demonstrable focus could not be recognized. Three of the six patients followed considered themselves 50 per cent improved, and three stated that they were unimproved. None can be classified in either of the "success" groups 3 and 4.

Two patients have died of intercurrent disease since operation, but their follow-up records of two and four years, respectively, are included.

EARLY CASES [8]

Fourteen patients have been followed for periods varying from six to 11 years. These were the first to be operated on in this series, and the results are summarized in table 3.

TABLE 3.—*Results of 51 Excisions of the Temporal Lobe 1 to 10 Years after Operation*

Groups	Cases		
0 No improvement	7	13.7%	21.5% Failure
1 Slight improvement	4	7.8%	
2 "Improved 50%" or more	13	25.4%	25.4% Results worth while
3 "Cured," with one or more attacks before cessation	13	25.4%	52.9% Success
4 "Cured," with no attacks	14	27.4%	

These patients have had a comparatively long period after operation for evaluation of results. Although in most of them more than half of the temporal lobe was removed, there has been no evidence of alteration in behavior, no particular memory loss, no persisting aphasia and no defect in initiative or capacity for decision.

As indicated in table 2, one patient has been operated on a second time since the termination of this analysis. It was found that there was induration of the cortex in the remaining uncus and hippocampal gyrus. This was excised, and he has had no further seizures during the few months that have followed operation.

OPERATION AND EXTENT OF EXCISION

These operations have been carried out with local anesthesia, usually dibucaine (nupercaine®). In the earlier cases sleep was induced during

8. One of us (W. P.) operated on a patient with temporal lobe epilepsy in 1928, and occasionally carried out similar procedures during the next 11 years, but it was not until the introduction of electroencephalography into clinical practice that the importance and frequency of this type of focal seizure became evident.

closure of the wound by the administration of tribromoethanol solution U. S. P. More recently, thiopental sodium has been used intravenously for this purpose. Electrical stimulation of the cortex has been carried out invariably. In some cases this has produced the initial phenomena of the patient's habitual attacks. In such cases it served as a guide to excision.

Electrocorticographic studies have been carried out with the help of Dr. Jasper, and these have often acted as a guide to initial excision and sometimes have indicated that further excision should be carried out. At times this further excision has led the operator to unsuspected abnormal tissue.

In 32 cases half or more of the temporal lobe was removed and in 2 cases only the temporal tip (3 or 4 cm.) was excised. With these removals, the uncus was excised in 10 cases and the hippocampus in 2 cases. In this group, 32 patients have been followed up, and 50 per

TABLE 4.—*Lesions of the Temporal Lobe*

Lesion	Cases
Areas of atrophy (5 with cysts)	39
Traumatic scars (1 with cyst)	9
Abscess scar	1
Microgyria	1
Unclassified	2
No objective evidence of abnormality	3

cent of them fall in the "success" groups 3 and 4. Of the 10 cases in which the uncus was excised, success followed operation in 5.

In 23 cases the ablation may be described as circumscribed, and success followed 57 per cent of the procedures. The cortex of the insula was excised more or less completely in 4 cases, and 2 of the cases have been placed in "success" group 3.

NATURE AND CAUSE OF THE LESIONS

The lesions are listed in table 4. No significant difference in operative results appeared with this grouping, the proportion of successes being about 50 per cent. In group 6 excision was carried out on electrocorticographic evidence alone, and only one of the three cases was placed in group 3.

The cause could only be surmised in some cases, but when all the evidence was studied the conclusions were summarized in table 5. There was no significant difference in operative results in the different groups of cases as classified on an etiologic basis, except that when birth compression was clearly the cause the prognosis was to be considered somewhat better.

DURATION OF ATTACKS BEFORE OPERATION

Table 6 shows the relation of the duration of attacks before operation to the number of cases which fall in the "success" groups 3 and 4. The number of cases in each group is not sufficiently large to permit us to draw valid conclusions as to the influence of duration of seizures on the outcome of operation. But it might seem that comparison of group 1 with group 2 favors earlier operation.

MEDICATION

In all cases, before operation conservative therapy has been tried by the patient's own physician, using phenobarbital, diphenylhydantoin

TABLE 5.—*Causes of Lesions of the Temporal Lobe*

Cause	Cases	Percentage of Success
Nonpenetrating trauma	26	41.6
Birth compression	10	60
Febrile illness	6	50
Hemangioma	3	100
Penetrating trauma	2	....
Brain abscess	1	....
Previous operation	1	....
Undetermined cause	6	40

TABLE 6.—*Preoperative Duration of Temporal Lobe Seizures*

Years	Cases	Cases Followed	Percentage of Success
1 or less	8	7	71
1- 5	14	11	54.5
6-10	19	16	56
11-15	3	3	100
16-20	8	8	50
Over 20	5	5	0

and often other drugs. Only when these procedures failed, and when normal life seemed impossible to achieve by less radical means, has surgical treatment been undertaken.

After operation, all patients are given phenobarbital, 2 or 3 grains (0.12 Gm. to 0.195 Gm.) daily, and no other medication. On discharge they are instructed to reduce the dose of phenobarbital gradually over a period of a year or two, if all goes well, and with the advice of the family physician.

At the time of this review, information regarding postoperative medication was available in the case of 44 patients. Eleven are taking no medication; 17 are on reduced amounts of phenobarbital, and 16 are receiving as much medication as before operation.

ROENTGENOLOGIC ABNORMALITIES

Roentgenographic study is often of great help. Smallness of the cranial chamber on one side is a strong argument in favor of an ischemic birth lesion on that side. Pneumoencephalography often shows enlargement of the inferior horn on the side of a lesion of the temporal lobe, but this can be no more than confirmatory evidence. The pneumoencephalograms suggested comparative abnormality on the side of the lesion in 37 cases and in the opposite temporal lobe in 6 cases. In 12 cases pneumoencephalography gave no lateralizing evidence.

When only the 27 cases which were eventually placed in the "success" groups were considered, the pneumoencephalogram was considered to indicate abnormality of the temporal lobe, which was later shown to contain the epileptogenic lesion in 18 cases. In 3 cases it seemed to point to the opposite side, and in 6 there was no lateralizing evidence.

ATTACK PATTERNS

In 20 cases there were attacks of automatic behavior. In 16 cases there were psychical illusions or hallucinations. In 13 cases there was an auditory or vestibular aura; in 5 cases, an olfactory or gustatory aura. There was no essential difference in the results of operation among these groups.

PRODUCTION OF AURA BY STIMULATION

An attempt is invariably made to reproduce each patient's initial seizure phenomena by electrical stimulation of the exposed brain. We have believed this to be important, and we sometimes carry out excision on this evidence alone. In the 19 cases in which the patient's aura was produced, the incidence of success was at any rate a little higher (63 per cent) than in the other 32 cases (47 per cent), in which stimulation failed to produce it.

CONCLUSIONS

Temporal lobe seizures, produced by focal lesions, may be treated by surgical ablation. The present analysis of 65 such operations occurring over a ten year period indicates that this is a most encouraging field of therapy.

PATTERNS IN ALLESTHESIA AND THEIR RELATION TO DISORDER OF BODY SCHEME AND OTHER SENSORY PHENOMENA

MORRIS B. BENDER, M.D.
AND
MORTON NATHANSON, M.D.
NEW YORK

IN RECENT communications one of us (M. B. B.) and associates [1] have described unusual sensory changes in patients with diffuse disease of the brain. These changes were unilateral allesthesia, or crossed displacement; extinction of sensation, and disturbances in location and identification of parts of the body. All these dysfunctions were found to be on one side of the body and were associated with severe mental disorder. Analyses of the responses to stimulations made in the affected sensory field disclosed that the defects were more pronounced in one area than in another. Thus, allesthesia, as well as extinction, was found oftenest in an extremity and seldom in the face. Extinction was more likely to occur in the distal than in the proximal portion of an extremity.[1c] These spatial differences were observed on repeated examinations. Moreover, under the influence of amobarbital sodium (amytal sodium®) the area which yielded allesthesia and extinc-

From the Department of Neurology and Psychiatry, New York University–Bellevue Medical Center.

This investigation was supported (in part) by a research grant from the National Institute of Mental Health, United States Public Health Service.

1. (*a*) Bender, M. B., and Wortis, S. B.: Patterns in Perceptual, Motor and Intellectual Functions in Organic Brain Disease, Tr. Am. Neurol. A. **72**:31, 1947. (*b*) Bender, M. B.; Wortis, S. B., and Cramer, J.: Organic Mental Syndrome with Phenomena of Extinction and Allesthesia, Arch. Neurol. & Psychiat. **59**:273 (March) 1948. (*c*) Bender, M. B.; Shapiro, M. F., and Teuber, H. L.: Allesthesia and Disorder of the Body Scheme, Tr. Am. Neurol. A. **73**:170, 1948. Shapiro, M. F.; Teuber, H. L., and Bender, M. B.: Disturbance of Body Image and Allesthesia, J. Nerv. & Ment. Dis. **108**:253, 1948. Bender, M. B.; Shapiro, M. F., and Teuber, H. L.: Allesthesia and Disturbance of the Body Scheme, Arch. Neurol. & Psychiat. **62**: 222 (Aug.) 1949.

tion enlarged, so that, instead of one extremity, an entire half of the body became involved. All these patients showed mental symptoms characteristic of an "organic" psychosis. They all had clinical evidence of diffuse disease of the brain. In two cases autopsy showed bilateral diffuse cerebral damage. In another case biopsy of the brain revealed Alzheimer disease (presenile sclerosis), and in a fourth, a diffuse arteriolar type of cerebral disease.

The experience gained in studies of this syndrome led us to investigate the aforementioned sensory phenomena from the standpoint of topographic distribution. In addition, we studied the relation of disorders of the body scheme, allesthesia, extinction and ipsilateral displacement of sensation.

A detailed report of a case history follows.

REPORT OF A CASE

J. L. M., a right-handed Negro aged 43, whose main occupation was that of a dancer, was admitted to the Bellevue Psychiatric Hospital on Dec. 22, 1947, having been transferred from the Harlem Hospital with the diagnosis of "schizophrenia." In August 1947 the patient began to complain of transient epigastric discomfort, poor appetite and visual disturbances, the nature of which was not clear. He said, "I just didn't seem to see right." His mother noticed that he "acted peculiar" and that his memory was failing. She also noticed that he had difficulty in recognizing and using certain objects. For example, when eating, he would use the handle of the knife in cutting meat, or he would hold the fork inverted. He often mistook the kitchen or living room for the bathroom. His mother said, "He seems all mixed up." This "confusion" became progressively worse, and he was finally taken to Harlem Hospital on December 13. Although he had been drinking sporadically since 1932, he denied ever having been hospitalized for alcoholism.

Physical Examination.—Except for many large, oval blueblack lesions of the skin over the trunk and extremities, the general physical examination showed essentially nothing unusual. Several of the lesions were ulcerated and crusted. A biopsy of the cutaneous lesions was reported to show "chronic dermatitis." The cause of these lesions was not determined.

Laboratory Data.—The results of all blood studies, including Wassermann and Mazzini tests, determination of the sugar, total protein and bromide levels and a cell count and smear, were within normal limits. A lumbar puncture revealed no gross chemical or serologic abnormalities. Roentgenograms of the skull and chest were reported as showing nothing abnormal. An electroencephalogram showed abnormal cortical activity in the right temporal and parietal regions. A pneumoencephalogram revealed dilated ventricles and a definite increase in cortical markings throughout. An etiologic diagnosis could not be made.

Psychiatric Status.—The psychiatric report on admission described the patient as disoriented, confused and apathetic. His affect was flat. His speech was slightly incoherent and at times unintelligeble. He denied having hallucinations or delusions. Several days after his admission to the hospital he was found to be more coherent

and less confused. He was cooperative and made strenuous efforts to answer questions and carry out commands. There was little spontaneous speech. When he spoke, he was hesitant and uncertain in his utterances. He appeared depressed and somewhat bewildered. Despite this appearance, he stated, "I'm not sad, but happy that people are trying to straighten me out." He was disoriented as to time and place. He showed denial of illness. Although he realized that he was a "sick man" and that "something was wrong," in many isolated situations he had no

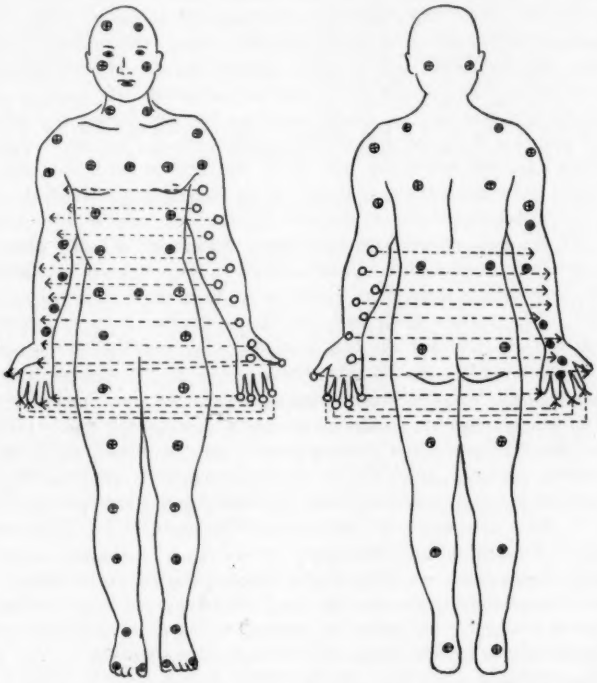


Fig. 1.—Schematic diagram of mislocalizations of single stimuli (allesthesia) from Dec. 29, 1947 through Jan. 6, 1948.

Plain circles indicate points of stimulation the sensation of which was mislocalized, as shown by arrows, to the opposite side of the body; circles containing a cross indicate points of stimulation correctly localized.

insight as to the presence or nature of his defects. Psychometric examination one week after his admission revealed a verbal score of 91 and a performance score of 72 on the Bellevue-Wechsler Scale. He showed gross inability to abstract, both verbally and in the various performance situations. His general information was good, but he was unable to use this knowledge to indicate the proper meaning of a given situation. When asked to relate the meaning of the well known proverb

"A rolling stone gathers no moss," he answered: "Moss is green, and it sticks to rocks." He made many errors in simple arithmetical problems, and he felt annoyed when he could not count backward from 20. Despite this, he denied having difficulties in calculation. His memory and retention for recent events were poor; he was unable to recall three digits after one minute, nor could he remember the date even after it was repeated for him several times during the interviews. The clinical psychiatric impression was "organic mental syndrome," possibly dementia paralytica.

Neurologic Status.—Routine neurologic examination revealed the following significant abnormalities: Both pupils reacted sluggishly to light. There was a left homonymous field defect on gross confrontation tests. On repeated occasions it was found that the patient was unable to look to the left on command but could do so on pursuit. The patient understood the command. He made an effort to turn to the left, but his eyes never moved to the left beyond the midposition. Mimetic weakness of the left side of the face was noted. There were slight weakness of the hand and downward drift of the outstretched upper extremity on the left. There was a constant coarse tremor of the fingers of the left hand. The gait showed diminished arm swing on the left. Except for a relative depression of the ankle jerks, the deep reflexes were hyperactive throughout. Routine sensory status showed defects in point localization of sensation in the left upper extremity. This mislocalization became much more evident when methods of simultaneous stimulation were used. In fact, many more defects in sensation were uncovered. Batteries of tests given during the first nine days of hospitalization disclosed three major sensory disorders, namely, allesthesia, extinction and body disorientation.

I. Allesthesia: When a single stimulus (pinprick) was applied to various regions of the left upper extremity (from the midarm on the flexor surface, and from the elbow on the extensor surface, down to the tips of the fingers), the patient stated that the sensation was present in the homologous area of the right upper limb (fig. 1). For example, pinprick of the left little finger was reported as a "pin" felt in the right little finger, or stimulation of the dorsum of the left wrist was reported as pinprick on the right wrist. These crossed, or contralateral, mislocalizations occurred even when the patient looked at the point of stimulation. When samples of blood were taken from the antecubital vein on the left, he was asked where he was "stuck." He replied by pointing to the right antecubital fossa just as the needle was being withdrawn from the vein on the left side.

Crossed mislocalizations also occurred when the vibration sense was tested in the left upper limb. All applications of a vibrating tuning fork to his left hand, fingers, wrist or elbow were reported as a "buzz" in the homologous areas on the right. Position sense in the left hand was markedly impaired. Tests for stereognosis gave the following results: He was aware of an object placed in his left hand, such as a match book but could not describe or name it. When asked to look at it, he would open his right hand and say, "I have nothing in my hand." When told he was given something, he answered, "You must have taken it back."

This crossed mislocalization of a single stimulus from one side of the body to the homologous area on the opposite side (allesthesia) was found only in tests of the left upper extremity (fig. 1) and persisted for nine days. Tests with single stimulation made over the other extremities, the trunk and the face showed no defects in localization.

II. Extinction Phenomena: A. Cutaneous: With the method of double simultaneous stimulation (pinprick) to homologous and nonhomologous areas of the trunk, face and extremities, the patient reported the following results:

Regions Stimulated Simultaneously	Report and Indication of Stimuli by Patient
Ieft and right cheek	Correct
Left and right breast	Correct
Left and right shoulder	One pinprick on right shoulder
Left and right arm	One pinprick on right arm
Left and right wrist	One pinprick on right wrist
Left and right hand	One pinprick on right hand
Left and right thigh	One pinprick on right thigh
Left and right leg	One pinprick on right leg
Left and right foot	One pinprick on right foot
Left cheek and left upper extremity	One pinprick on left cheek
Left upper extremity and left lower extremity	One pinprick on left lower extremity
Left cheek and right upper or lower extremity	Correct
Right cheek and left upper or lower extremity	One pinprick on right cheek

In summary, stimulations using pinprick to the left upper and lower extremities did not elicit responses when simultaneous stimuli were applied to other parts of the body. Double simultaneous stimulations of the face (both cheeks) or trunk were always reported correctly as two pinpricks, one on each side of the face or trunk. Extinction phenomena were obtainable over a period of many weeks. On or about the twelfth week we observed a different phenomenon, namely, that of displacement. The observations concerning the phenomenon of displacement will be described in the subsequent course of his illness.

B. Visual: Examination of visual functions also revealed extinction phenomena. However, there was no visual allesthesia.

1. Gross confrontation tests: (*a*) Single stimulation. A single stimulus object in motion, such as the examiner's hand, was promptly seen when moved in any part of the field of vision, except in the lower left homonymous quadrants. Nevertheless, he showed defects in the left homonymous half-fields of vision when he was asked to identify single objects, such as a pen or a book of matches, which were not in motion. He was always accurate in the right fields of vision. Similarly, when he was asked to touch an object presented in the left half-field of vision while looking at a central fixation point, he groped and often could not locate it. His localization in the right field of vision was always correct.

(*b*) Double stimulation. Bilateral simultaneous stimulations elicited responses only in the right homonymous half-fields of vision. There was extinction of vision in the left half-fields.

2. Perimetric tests: Perimetric and tangent screen examinations revealed defects in the left homonymous half-field for a moving target (fig. 2). This was more pronounced in the left lower quadrants. Color fields could not be plotted with any degree of accuracy.

3. Special tests: (*a*) Tachistoscopic examination. Tests with the tachistoscope corroborated the presence of a left homonymous field defect. A slide showing five similar figures, one in each quadrant of the field of vision and one in the center, was flashed on a screen for 1/25 second. The figure identified by the patient was

the one in the center. On further exposure at 1/25 second, he usually named the figures in the center and in the right field. He did not report, or he "ignored," those in his left field. With longer exposures, 1/5 and 1/2 second, or on continuous exposure, he still did not mention the presence of figures in his left field. Slides showing drawn figures of a face with a missing ear or a body with a missing limb were flashed on the screen for 1/2, 1 and 2 second intervals. He named the figures correctly. However, he could not detect the omission in the face or body when the defective parts of the figure were exposed in his left field of vision. When the projected images were reversed and the defective side of the figure was situated in his right field of vision, he noted the omissions promptly at one second exposures.

(*b*) Wool-sorting test. This test elicited defects in his left field of vision. The patient was able to identify all the colors of the wool skeins. When the wool skeins were scattered evenly in his entire field of vision and he was asked to pick out certain colors, the selections in his right field of vision were accurate and much more numerous than those in his left field. Other sorting and grouping tests

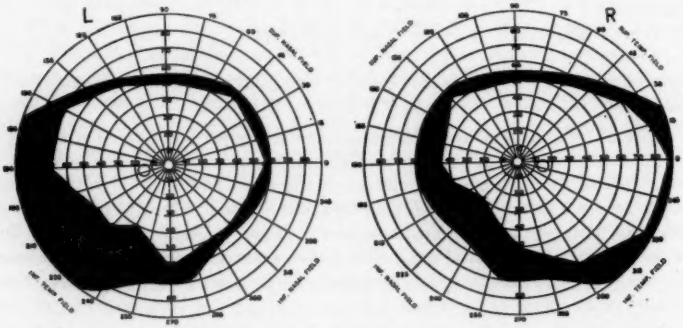


Fig. 2.—Perimetric fields. A 10 mm. moving target under standard illumination was tested at a distance of 33 cm. from the eye. The black area indicates the zone in which the target was not perceived.

revealed similar dextrotendencies with "neglect" of objects situated in his left field of vision.

(*c*) Field of search test. The patient was asked to fix a target, a cross, approximately 1 meter from his eyes. Surrounding the target were different-colored geometric figures, numbers and letters of the alphabet, arranged at random on a screen. The area of the screen was 16 square feet (14.9 square meters). He was given single cards, each of which showed an exact duplicate of one of the figures in the areas surrounding the target. He was then asked to find the figure on the screen. The cards with figures requiring localization in his left field of vision took him more than twice the time required by those calling for localization in his right field of vision. There was always difficulty in finding the figure in his left field, and occasionally he gave up in despair, thus failing in his task.

(*d*) Reading and writing. Other disorders in perception were manifest in reading and writing. The patient could read and understand simple words and sentences, but it was noted that he usually held the reading material in his right field of vision. When he was given a pencil and paper and instructed to write, it was observed that he invariably adjusted the paper so that the left border was in his

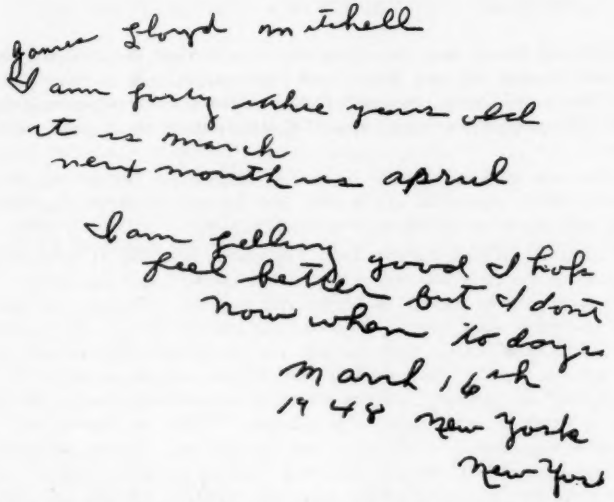
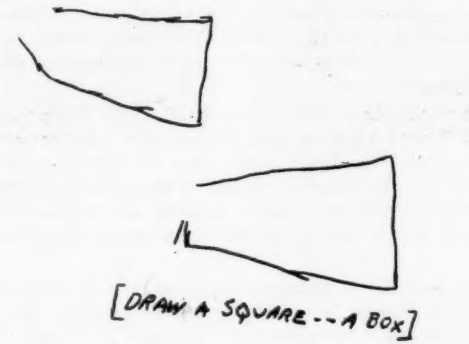


Fig. 3.—Sample of handwriting. Note the tendency to displacement of the handwriting to the right.



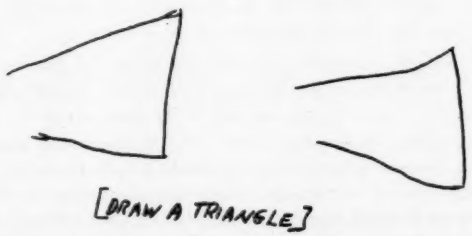


Fig. 4.—Sample of the patient's attempts to draw geometric figures. He constantly omitted lines or points of closure in his left field of vision.

central field of vision, thus placing the sheet in his right field. Every sentence began about ½ inch (2.5 cm.) closer to the right margin, until he could write only two or three words before the right border of the sheet of paper was reached (fig. 3). This pattern in writing, a type of disorientation in visual space, existed for six months.

He was able to draw a circle, but it was difficult for him to complete such angular geometric figures as a triangle. The incomplete side of the geometric drawing was usually in his left field of vision (fig. 4).

III. Disorders in Body Orientation: The patient was able to name the parts of his body on the right side and in the midline promptly and accurately. When asked to name parts of his body on his left side, however, he became confused, was hesitant and made many errors. When he was asked to show a hand, an ear or any part of his body and the particular side was not specified, he invariably showed the parts on his right. When asked to point to the homologous part of the body on the "other," or "opposite," side, he looked about searchingly and again showed the part of the body on the right. For example: ("Show me your thumb.") He indicated his right thumb. ("Show me your other thumb, your left thumb.") He again showed his right thumb and remarked, "Here is my other thumb." ("How many thumbs do you have?") He answered, "Two." ("Show me your two thumbs.") He showed only his right thumb. The command "left" or "right" did not seem to have meaning to the patient. He always replied by indicating his right side. For example: ("Show me your left elbow.") He pointed to the right elbow. ("That is your right elbow; now show me your left elbow.") He hesitated and again pointed to his right elbow. This dextrotendency was also evident in tests of the lower extremities and of the paired structures of the face, but to a less pronounced degree.

In conjunction with the disorder in the body scheme, it was observed that the extrapersonal space on his left side was also defective. He "ignored" the environment on his left side. The latter defects were described in part under various tests, particularly those dealing with vision. It should be noted that the disorder in the body scheme was part of a massive disability in sensorimotor and conceptual performances when the left side of his body or the extrapersonal space on that side was tested.

Course in Hospital.—This syndrome was found on repeated tests for nine days (from Dec. 29, 1947 through Jan. 6, 1948). On the tenth day there was improvement. He was then able to recognize and locate parts of his body to some extent. The mislocalization of cutaneous stimuli, i. e., allesthesia and difficulty in visual performances, also diminished. The allesthesia lessened in frequency of response and in area. Allesthesia was now confined to the palmar surface of the left hand and the dorsal surface of the fingers. Localization of single stimuli in the left arm and forearm was correct (fig. 5). He was now able to indicate and identify parts of his body on either side, but he still made errors on the left.

Extinction of cutaneous sensation, however, persisted. The left visual field defect could be elicited only by double simultaneous stimulation. Single test targets were correctly localized and named in any one part of the field of vision.

Examinations Under Amobarbital (Amytal®) Sodium.—On the eleventh day the allesthesia was present in tests of the tips of the fingers of the left hand. Moreover, for the first time he mislocalized single stimuli applied on the toes of the left foot to the corresponding toes of the right foot. After 0.3 Gm. of amobarbital sodium was given intravenously, the sensory areas from which allesthesia was

obtained increased. In the left upper limb this area extended proximally to the midarm on the flexor surface and to the elbow on the extensor surface. In the left lower extremity the area from which allesthesia was obtained spread to the knee on the extensor surface and up to the midthigh on the flexor surface (fig. 6). Because of the ataxia produced by the amobarbital sodium it was difficult for the patient to make exact localizations in tests of each toe. There was increase in his inability to name or to point out parts of his body on his left side. The patient appeared upset and bewildered when he was asked to show his left hand or left arm. He responded with uncertainty in his movements and referred or mis-

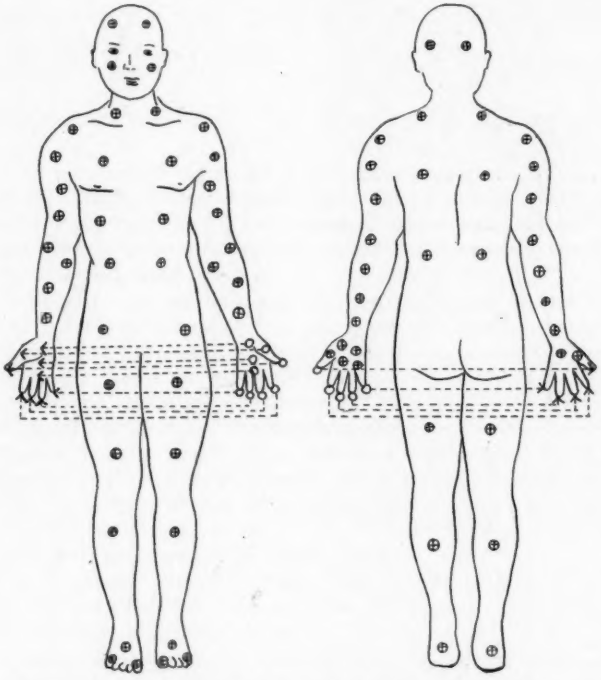


Fig. 5.—Decrease in degree of allesthesia, Jan. 7, 1948 (symbols same as in figure 1). Note that the recession of the sensory disorder is in a distal direction, being more advanced on the dorsal than on the palmar surface of the hand.

localized to parts of the body on his right side only. There were no errors when parts on the right side of his body were tested. The cutaneous extinction effects on the left side were just as severe as those prior to the injection of amobarbital.

Shortly before the effect of the amobarbital had worn off, he was given his pajama pants and told to put them on. He obeyed and attempted to put them on as one would a sweater, placing a hand in each trouser leg and covering his head with the crotch of the trousers.

Two hours after the amobarbital sodium had been injected the area from which allesthesia could be obtained decreased to the original extent.

The following morning, on the twelfth day, the allesthesia could no longer be elicited, and there was a definite improvement in body orientation. However, the cutaneous extinction phenomenon persisted with no modification. He still showed preference for his right field of vision with double simultaneous stimulations.

The subsequent course showed the following changes in the sensory responses:

1. Phenomenon of displacement. The patient gradually improved. For the first eleven weeks tests with the method of double simultaneous stimulation revealed extinction on the left side, but after this period the responses began to vary. This became apparent when nonhomologous parts on the two sides of the body were

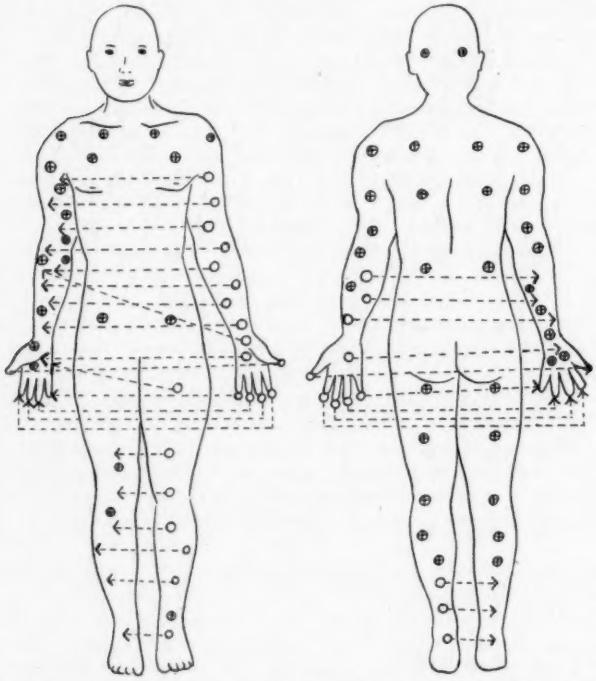


Fig. 6.—Increase in area of allesthesia after intravenous injection of 0.30 Gm. of amobarbital sodium on Jan. 8, 1948 (symbols same as in figure 1).

tested. Whereas in previous stimulations of the left hand and the right cheek the patient reported sensation only in the right cheek, the patient now reported two sensations and indicated them as one on each cheek. Evidently, both stimuli were perceived, but that on the left hand was displaced to the left cheek (at the level corresponding to the stimulus applied on the right). This we have called the phenomenon of ipsilateral displacement.[2] Displacement and extinction were not

2. Bender, M. B.; Shapiro, M. F., and Schappell, A. W.: Observations on the Extinction Phenomenon in Hemiplegia, Tr. Am. Neurol. A. **74**:160, 1949; Extinction Phenomena in Hemiplegia, Arch. Neurol. & Psychiat. **62**:717 (Dec.) 1949.

observed when homologous parts on the two sides of the body were simultaneously stimulated. The following tabulation is a summary of a series of tests:

Regions Stimulated Simultaneously	Report and Indication of Stimuli by Patient
Right cheek and left hand	Single pinpricks to right and left cheek
Left cheek and right hand	Single pinpricks to right and left hand
Right cheek and left elbow	Single pinpricks to right and left cheeks
Left cheek and right elbow	Single pinpricks to right and left elbow
Left hand and right hand	Correct
Left hand and right foot	Single pinpricks to right foot and left knee
Right hand and left foot	Single pinpricks to right and left hand
Right foot and left foot	Correct
Right cheek and left foot	Single pinpricks to right cheek and left cheek
Left cheek and right foot	Single pinpricks to right foot—(hesitation), left hand and then left knee

Thus on simultaneous stimulation of two nonhomologous regions, the patient displaced the sensation evoked by the stimulus on the left toward the level of the one evoked on the right side. This displacement phenomenon persisted for over two years. The cutaneous area in which displacement occurred oftenest was that of the left upper extremity.

2. Allesthesia. For several weeks after the amobarbital sodium interview there were no signs of allesthesia. On January 25 new observations were made, using the method of alternating pinpricks. Pinprick stimulations of homologous areas on the two sides of the body were made a fraction of a second apart. When the left hand and, within the next second, the right hand were stimulated, the patient reported that he felt two repeated pricks on the right. When the alternation was begun on the right—pinprick to the right hand being followed immediately by pinprick to left hand—he reported correctly that he felt two pinpricks, one on each side. This phenomenon, a form of allesthesia, was noted in tests of the upper extremities, but not of parts of the rest of the body. It was elicited for four consecutive days, and thereafter its presence fluctuated from time to time during our follow-up studies. However, all the mislocalizations with this method were confined to the left forearm, wrist and hand and were more consistent on the flexor surface than the extensor surface.

3. Disorders in recognition of parts of body. During the period when the patient showed maximum disturbance in cutaneous perception, there was mislocalization of parts of his body on his left side to his right side. Although he maintained that he had two hands or two thumbs, he reported they were both on the right side. Frequently he was positive in his response. Unlike true autotopagnosia, in which the existence of one side or part of one side of the body is denied, this patient acknowledged the existence of his left side, but to him it was located on his right.

COMMENT

Our present case study shows a number of significant facts. Sensory changes can be elicited in the psychotic patient. The sensory changes are patterned and limited in extent. Sensation evoked by stimuli in the

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affected region is unstable. Such sensations are variable in threshold, as well as in localization, and are always influenced by stimuli applied simultaneously in other regions of the body. This influence is especially noticeable when the simultaneous stimuli are applied in normal regions of the sensory field. A stimulus applied on the normal side will cause extinction or displacement of sensation simultaneously evoked on the affected side. These very sensory phenomena can be accentuated in degree and in extent by the intravenous administration of subanesthestic doses of amobarbital sodium.

Among the many disturbances in function which our patient showed, the most prominent were (*a*) displacements of sensation, (*b*) extinction of sensation and (*c*) inability to recognize, identify or associate sensations or acts which occurred on the left side of his body and the surrounding, or extrapersonal, space on his left side. The patient showed inability to cope with situations which involved the left side of his body or his left sensory space. In fact, all these disorders were so severe that they made the patient appear more confused than he actually was. There was no doubt that he had defects in intellectual functions, but the concomitant distortions in sensorimotor performances produced a bizarre mental picture. Within this "mental confusion" it was apparent that the patient avoided, ignored and turned away from objects on his left side. It was as though all performances on his left were dominated by those on his right and this dominance forced him to turn away from the left side. In fact, all sensorimotor performance in the affected, left field was always influenced by stimuli applied concomitantly in the right sensory field.

A significant finding was that all these disorders—allesthesia, extinction and sensorimotor imbalance—showed a pattern when tests of different regions of the body were compared. Under the influence of amobarbital sodium, the pattern became more apparent, and the extent of disorder was increased in a definite direction. The spread of area from which defects could be obtained was from distal to more proximal portions of the limb. As the effect of the drug began to wear off, the extent diminished in a reverse direction; that is, allesthesia and disorders of body scheme began to disappear on the left side of the trunk and the proximal portions of the left limbs and ultimately remained in the distal parts of the left upper extremity.

The change in pattern which occurred when the patient was rapidly recovering from the influence of amobarbital sodium was similar to the change in pattern we observed when the patient was slowly recovering during his convalescent period. Another feature was that the degree of sensory imbalance between the two sides of the body varied with the severity of cerebral dysfunction. The severer the mental changes, the

more pronounced were the disorder in body scheme and the allesthesia. Extinction and displacement of sensation may be found with or without mental changes. They have been described in the normal adult and are particularly evident in the young child.[3] Extinction and displacement are more conspicuous in patients with an organic mental syndrome. The degree of the sensory defects varies with the severity of the mental changes.

As to the cerebral localization of the various disorders of sensation found in this patient, we have no data. A pneumoencephalogram showed what appeared to be diffuse atrophy of both sides of the brain. The fact that there were marked defects in sensorimotor function on the left side of the body would imply greater damage to, or a large lesion in, the right cerebral hemisphere. Such a deduction, however, cannot be substantiated by anatomic studies made in similar cases. In a previously reported case in which the patient showed almost the same type of sensorimotor dysfunction, but on the right side of her body, detailed gross and histologic studies of the brain showed diffuse involvement of both cerebral hemispheres and of the entire corpus callosum.[1e] There was no evidence that one hemisphere or such parts as the thalamus or the internal capsule were implicated on one side more than on the other.

Nevertheless, there are cases in which clinicopathologic studies show that extinction of sensation on one side of the body, or even in one extremity, can be produced by a localized lesion in the brain. Kolb studied two cases in which surgical excision of brain tissue within the parietal lobe produced subsequent extinction.[4] In fact, a lesion anywhere along the spinothalamic or the thalamoparietal system may produce a change in sensory function which, on special testing with the methods of double simultaneous stimulation, will yield extinction. The same may be said of allesthesia. However, in allesthesia severe mental changes characteristic of diffuse disease of the brain are often found. The only possible exception is in cases of tabes with marked sensory defects, as a result of a lesion of the spinal cord. Careful analyses of these cases, however, shows that the displacement of sensation is never orderly or systematic to one side.[5] The displacement may be ipsilateral and occur

3. Bender, M. B.; Fink, M., and Green, M.: Patterns in Perception on Simultaneous Tests of Face and Hand, Tr. Am. Neurol. A., 1950, to be published.

4. Kolb, L.: Observations on the Somatic Sensory Extinction Phenomenon and the Body Scheme After Unilateral Resection of the Posterior Central Gyrus, Tr. Am. Neurol. A., 1950, to be published.

5. We have not found true allesthesia in a patient with tabes. On the other hand, we observed all types of displacement, including allesthesia and synesthesia, in a patient with sensory changes as the result of a tumor of the spinal cord.

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along the vertical axis of the body in an unpredictable fashion. Moreover, the displacement is frequently a synesthesia, thus yielding a picture of two sensations evoked by a single stimulus.

As for localization of defect in perception of parts of the body and space, one might refer to the studies of Schilder[6] and Gerstmann.[7] These authors have described cases in which a lesion in the parieto-occipital region, including the supramarginal and angular gyri of the dominant hemisphere, produced disorder in the "body image" and right-left disorientation. The disturbances in body image were bilateral, and the spatial disorientation was on either side of the body. In our case, however, the disorders in recognition of parts of body and spatial orientation are predominantly unilateral, i. e., on the left side.

These features, together with allesthesia and extinction, comprise a syndrome which is far different from the one reported by Gerstmann. What we wish to stress in our case is not only the syndrome described, but the spatial pattern which the allesthesia and other disturbances assumed with a decrease in symptoms when the patient improved spontaneously and with an increase in symptoms when he was under amobarbital narcosis.

In diffuse disease of the brain one may see a pattern in which one side of the body becomes dependent on, or is influenced or dominated by, the other. What determines such a pattern remains a mystery. However, this mystery is not greater than the question as to what determines patterns in normal function.

SUMMARY

A case of an "organic mental syndrome" with bizarre behavior and severe confusion is reported. Within this picture it was possible to elicit clearcut changes in sensation. Using a variety of tests, unilateral disorders in sensation, such as extinction, allesthesia and other types of displacement of sensation, were found. Errors or lack of response was found always on the left side, more particularly in the upper extremity.

It was found that the pattern of cutaneous allesthesia is similar to that of any other sensory dysfunction seen in patients with disease of the brain. Emphasis is placed on the coexistence of mental changes and disturbances in orientation of the body and adjacent sensory space when allesthesia is present. This fact is corroborated by observations made

6. Schilder, P.: Mind: Perception and Thought in Their Constructive Aspects, New York, Columbia University Press, 1942.

7. Gerstmann, J.: Fingeragnosie und isolierte Agraphie, ein neues Syndrom, Ztschr. f. d. ges. Neurol. u. Psychiat. **108**:152, 1927; Zur Symptomatologie der Herderkrankungen in der Uebergangsregion der unteren parietal- und mittleren Okzipitalhirnwindung, Deutsche Ztschr. f. Nervenh. **116**:46, 1930.

during the patient's spontaneous improvement and while he was under the influence of amobarbital (amytal®) sodium, administered intravenously. Besides the patterns of the individual phenomena, there seems to be an over-all order of the entire clinical picture.

Discrete cerebral localization in this case was not possible. Although others have claimed the thalamus and parietal lobe to be the seat of many of these dysfunctions, we have no data to support such contention. In our case the pneumoencephalogram showed diffuse atrophy of the brain. Moreover, detailed anatomic study of a similar case showed bilateral diffuse disease of the brain.

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EFFECT OF TREATMENT ON EXCRETION OF 17-KETOSTEROIDS IN PATIENTS WITH MENTAL DISEASE

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AND
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A CONSIDERABLE body of evidence now exists showing that hematologic and chemical changes indicative of alterations in function of the adrenal cortex occur in patients receiving shock treatment for psychosis.[1] Published data on the excretion of 17-ketosteroids are some-

From the Laboratory of Clinical Physiology, McLean Hospital, and the Department of Medicine, Harvard Medical School, Boston.

1. (*a*) Gross, M.: Insuline et schizophrenie, Schweiz. med. Wchnschr. **17**:689, 1936. (*b*) Harris, A.: Cardiazol Treatment of Schizophrenia, J. Ment. Sc. **84**:735, 1938. (*c*) Katzenelbogen, S.; Harms, H. E.; Williams, R.; Barkoff, S.; Brody, M. W., and Harpman, M.: The Insulin Treatment in Schizophrenic Patients: Clinical and Biochemical Studies, Am. J. Psychiat. **95**:793, 1939. (*d*) Mikkelsen, W. P., and Hutchens, T. T.: Lymphopenia Following Electrically Induced Convulsions in Male Psychotic Patients, Endocrinology **42**:394, 1948. (*e*) Altschule, M. D.; Altschule, L. H., and Tillotson, K. J.: Changes in Blood Leukocytes in Man After Electrically Induced Convulsions, Arch. Neurol. & Psychiat. **62**:624 (Nov.) 1949; (*f*) Changes in Urinary Uric Acid-Creatinine Ratio After Electrically Induced Convulsions in Man, J. Clin. Endocrinol. **9**:548, 1949. (*g*) Parsons, E. H.; Gildea, E. F.; Ronzoni, E., and Hulbert, S. Z.: Comparative Lymphocytic and Biochemical Responses of Patients with Schizophrenia and Affective Disorders to Electroshock, Insulin Shock, and Epinephrine, Am. J. Psychiat. **105**:573, 1949. (*h*) Altschule, M. D.; Parkhurst, B. H., and Tillotson, K. J.: Decreases in Blood Eosinophilic Leukocytes After Electrically Induced Convulsions, J. Clin. Endocrinol. **9**:440, 1949. (*i*) Altschule, M. D.; Ascoli, I., and Tillotson, K. J.: Extracellular Fluid and Plasma Volumes in Depressed Patients Given Electric Shock Therapy, Arch. Neurol. & Psychiat. **62**:618 (Nov.) 1949. (*j*) Altschule, M. D., and Tillotson, K. J.: Effects of Electroconvulsive Therapy on Diuretic Response to Water in Psychotic Patients, ibid. **61**:188 (Feb.) 1949; (*k*) Effect of Electroconvulsive Therapy on Water Metabolism in Psychotic Patients, Am. J. Psychiat. **105**:829, 1949. (*l*) Altschule, M. D.; Cline, J. E., and Tillotson, K. J.: Fall in Plasma Protein Level Associated with Rapid Gain in Weight During the Course of Electroshock Therapy, Arch. Neurol. & Psychiat. **59**:476 (April) 1946. (*m*) Rees, L.: Physiological Concomitants of Electronarcosis, J. Ment. Sc. **95**:162, 1949. (*n*) Altschule, M. D.; Grunebaum, H., and Promisel, E.: Significance of Changes in Extracellular Fluid Volume During Insulin Therapy for Mental Disease, J. Applied Physiol. **2**:477, 1950. (*o*)

what discordant, in part because of the fragmentary nature of the observations; and therefore it seemed desirable to make a study of the changes which occur over a long period of time during the treatment of patients given psychotherapy, ambulatory insulin therapy or electric shock therapy.

MATERIAL AND METHODS

The patients studied during treatment are described in the accompanying table. Urine was collected for several days before and for varying periods during and after treatment. Other patients were studied during periods of one to three days while not receiving treatment. Urine was collected in each case for a succession of twenty-four hour periods. Collections of urine were discarded when found on analysis to contain less creatinine than the amount that was ordinarily found in

Data on Excretion of 17-Ketosteroids During Shock Treatment

Patient	Age	Sex	Diagnosis	Treatment	Changes in 17-Ketosteroid Excretion
F	32	F	Psychoneruosis; reactive depression	Psychotherapy	Early rise; late fall
W	34	F	Psychoneurosis	Psychotherapy	None
T	29	F	Psychoneurosis	Insulin	? Early rise; late fall
Mo	36	F	Manic-depressive, depressed	Insulin	Early rise (partial study)
Cu	43	F	Manic-depressive, depressed	Insulin Progesterone Electric shock	Early rise; no fall None Late fall
Co	52	F	Manic-depressive, depressed	Electric shock	None
R	39	M	Manic-depressive, depressed	Electric shock	Early rise; late fall
G	51	M	Manic-depressive, depressed	Electric shock	Early rise (partial study)
B	59	M	Manic-depressive, depressed	Electric shock	? Fall (partial study)
C	58	M	Manic-depressive, depressed	Electric shock	? Fall (partial study)
Ma	47	F	Manic-depressive, depressed	Electric shock	Early rise (partial study)
I	45	F	Schizophrenia	Electric shock	None
J	44	F	Schizophrenia	Electric shock	Fall
S	27	F	Schizophrenia	Progesterone	Rise
H	59	F	Schizophrenia	Porgesterone	No change

each case; the method of Folin [2] was used to measure the creatinine content of the twenty-four hour collections of urine. The method of Callow and associates [3] was used for measuring the 17-ketosteroid content of the urine.

OBSERVATIONS

Untreated Patients.—Sixty-nine determinations of the urinary excretion of 17-ketosteroids were made on untreated subjects. Of 12 mea-

Grunebaum, H., and Altschule, M. D.: Sodium Concentration of Thermal Sweat in Treated and Untreated Patients with Mental Disease, Arch. Neurol. & Psychiat. **63**:444 (March) 1950. (*p*) Hoagland, H.; Callaway, E.; Elmadjian, F., and Pincus, G.: Adrenal Cortical Responsitivity of Psychotic Patients in Relation to Electroshock Treatments, Psychosom. Med. **12**:73, 1950.

2. Folin, O.; Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1932, vol. 2, p. 602.

3. Callow, N. H.; Callow, R. K., and Emmens, C. W.: Colorimetric Determination of Substances Containing the Grouping -CH_3CO- in Urine Extracts as an Indications of Androgen Content, Biochem. J. **32**:1312, 1938.

surements made on severely neurotic women, 9 revealed values above 10 mg. per day. Of 44 estimations made on psychotic women, 4 were below 5 mg. and 9 were above 10 mg. per day. There was no difference between the values for patients with schizophrenia and those for patients with other psychoses, such as the manic-depressive or the involutional. Thirteen studies made on psychotic men revealed the excretion of more than 15 mg. per day in 12 instances (chart 1).

Effect of Psychotherapy.—Two patients received psychotherapy alone. One (case F, chart 2) was apathetic, anoretic and depressed to the

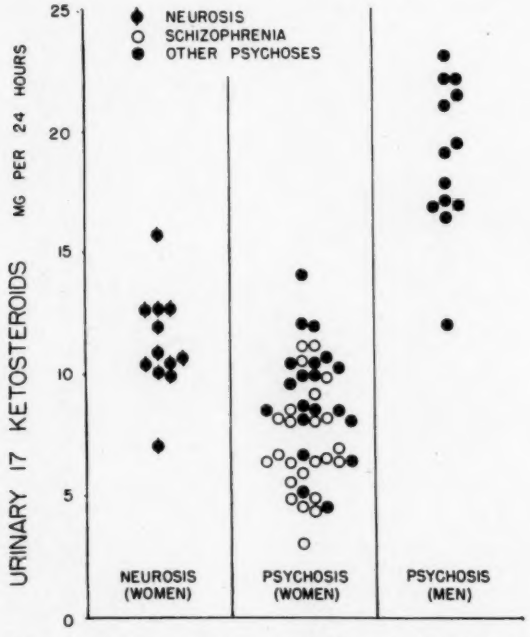

Chart 1.—Output of 17-ketosteroids in untreated patients.

point of muteness. She was seen daily by a psychiatrist; a friendly relationship between the two did not exist. After a few days she became more active, and her appetite returned; a rise in excretion of 17-ketosteroids was found during this period. After an interval she ceased to be depressed; during this time the average excretion of 17-ketosteroids fell to and then below the control level, in spite of the continued intake of a large diet. The second patient (case W, chart 2) was seen daily by a psychiatrist and, on the basis of her verbalizations, was considered somewhat improved; she showed no change in excretion of 17-ketosteroids.

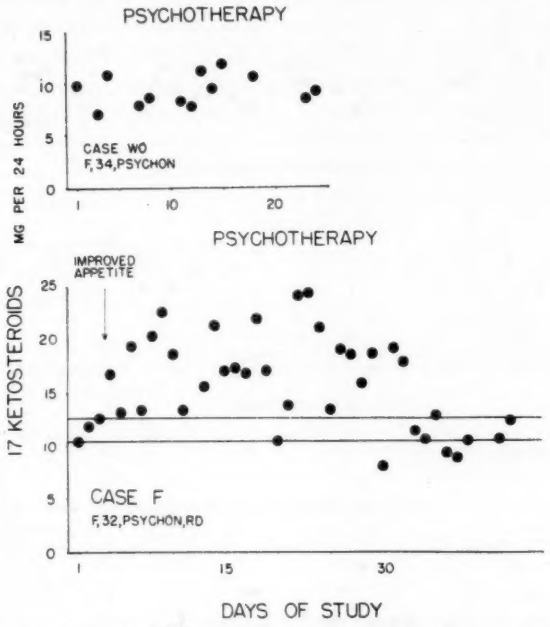

Chart 2.—Output of 17-ketosteroids in 2 women during psychotherapy.

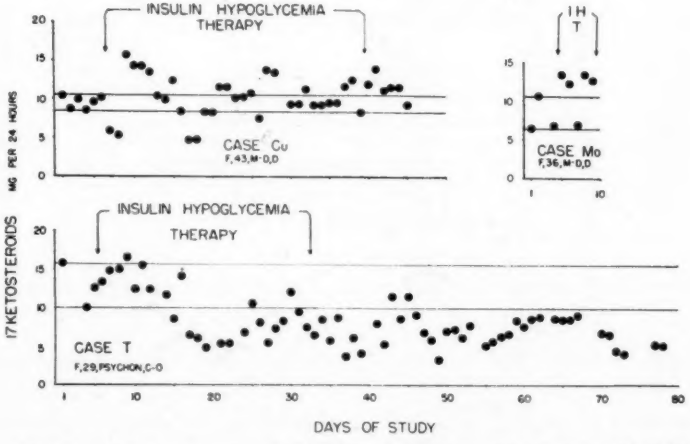

Chart 3.—Effect of a course of ambulatory insulin therapy on output of 17-ketosteroids in 3 women.

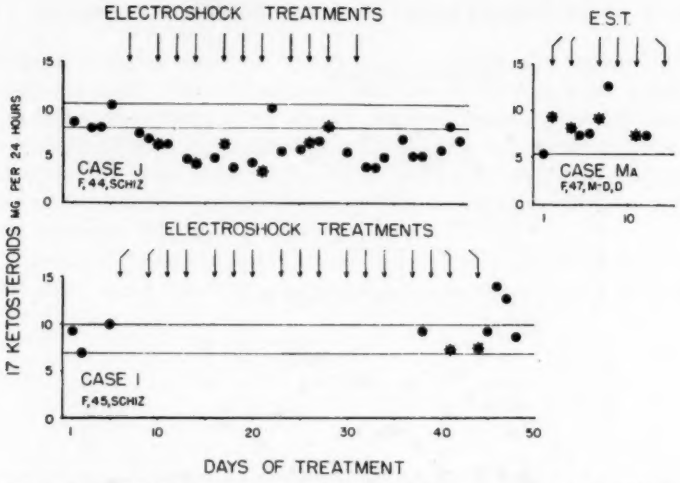

Chart 4.—Effect of a course of electric shock therapy on output of 17-ketosteroids in 3 women.

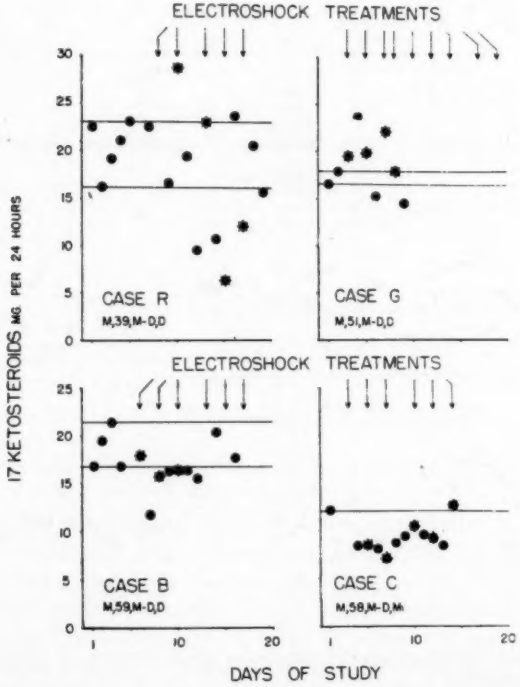

Chart 5.—Effect of a course of electric shock therapy on output of 17-ketosteroids in 4 men.

Effect of Insulin Therapy.—Three studies of the effect of insulin, 1 of them incomplete (case Mo, chart 3), were made. In each instance an early rise in the excretion of 17-ketosteroids occurred; this was definite in 2 patients (cases Mo and Cu, chart 3) and questionable in 1 (case T, chart 3). Patients Mo and Cu showed a striking increase in

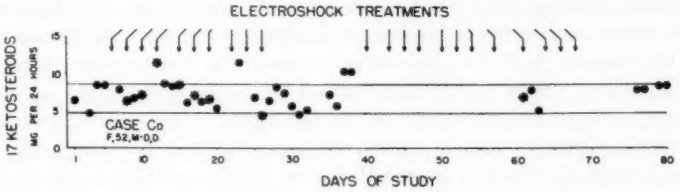

Chart 6.—Output of 17-ketosteroids in a woman who failed to respond to prolonged electric shock therapy.

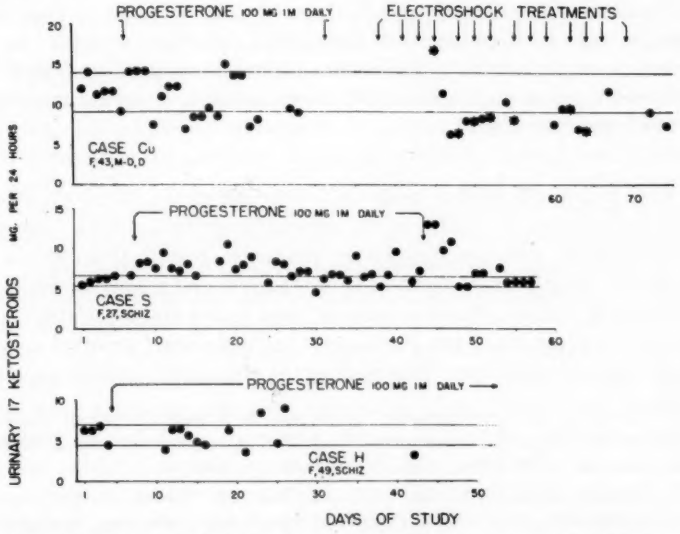

Chart 7.—Effect of administration of progesterone on output of 17-ketosteroids in 3 women.

agitation at this time, whereas patient T exhibited this change to only a slight degree. Two patients were followed through the entire course of treatment and for a period thereafter. One (case T, chart 3) exhibited a persistent decrease in excretion of 17-ketosteroids and was greatly improved clinically. The other (case Cu, chart 3) showed no decrease in excretion of 17-ketosteroids and no benefit from the treatment.

Effect of Electric Shock Therapy.—Nine patients were given electric shock therapy. In 7 of the 9 patients the study included the initial period of treatment; in 3 of 7 patients (cases Ma, chart 4; cases G and R, chart 5) an early increase in the excretion of 17-ketosteroids occurred. In 3 patients (cases J, R and Cu, charts 4 and 5) definite decreases in the average excretion of 17-ketosteroids occurred; the condition of all 3 patients was improved. In 2 others (cases B and C, chart 5) decreases probably occurred, but the data are not adequate for a definite conclusion in this respect; both the patients were improved. No decrease occurred in 2 patients (cases Co and F, charts 6 and 4). In 1 patient (case I, chart 4) there was definitely no improvement; in the other (case Co, chart 6), although she was considered improved after ten treatments, at which time she was very confused, it was found necessary to reinstitute treatment two weeks later and a total of twenty-three treatments did not result in improvement.

Effects of Progesterone.—Administration of progesterone U. S. P. to 3 patients (cases Cu, H and S, chart 7) did not result in improvement in any; no decrease in 17-ketosteroid excretion occurred. In 1 patient (case Cu, chart 7) electric shock given subsequently resulted in decreased average excretion of 17-ketosteroids and in clinical improvement of moderate degree.

COMMENT

The data of the present study show that the daily urinary excretion of 17-ketosteroids is usually in the normal range in psychotic patients and in patients with neuroses severe enough to require treatment in a psychiatric hospital; this observation is in accord with the earlier findings of Escamilla,[4] Hemphill and associates [5] and Simon and associates [6]; on the other hand, Ashby [7] and Friedlander and associates [8] reported values which tended to be low. The findings of the latter authors may be

4. Escamilla, R. F.: Diagnostic Significance of Urinary Hormonal Assays: Report of Experience with Measurements of 17-Ketosteroids and Follicle Stimulating Hormone in the Urine, Ann. Int. Med. **30**:249, 1949.

5. Hemphill, R. E.; MacLeod, L. D., and Reiss, M.: Changes in the Output of 17-Ketosteroids After Shock Treatment, Pre-Frontal Leukotomy and Other Procedures, J. Ment. Sc. **88**:554, 1942. Hemphill, R. E.: The Significance of Atrophy of the Testes in Schizophrenia, J. Ment. Sc. **90**:696, 1944.

6. Simon, A.; Bowman, K. M., and Halliday, N.: Studies on Electronarcosis Therapy: II. Physiological Effects in Electronarcosis and Electroshock, J. Nerv. & Ment. Dis. **107**:358, 1948.

7. Ashby, W. R.: The Effects of Convulsive Therapy on the Excretion of Cortins and Ketosteroids, J. Ment. Sc. **95**:275, 1949.

8. Friedlander, J. H.; Perrault, R.; Turner, W. J., and Gottfried, S. P.: Adrenocortical Response to Psysiologic Stress in Schizophrenia, Psychosom. Med. **11**:86, 1949.

accounted for on the basis of malnutrition; Landau and associates [9] have shown how even brief periods of starvation diminish the excretion of 17-ketosteroids, and Reiss [10] studied a patient with anorexia nervosa who excreted 6.9 mg. per day when weighing 54 pounds (24.5 Kg.) and 20.2 mg. per day when weighing 148 pounds (67.1 Kg.). In some patients in the present series the excretion was somewhat greater than the normal absolute value, and in many others the values obtained were elevated when the low caloric intake of the patients was taken into account.

Individual electric shock treatments were shown by Simon and associates [6] and by Ashby [7] to be without consistent effect on the output of 17-ketosteroids, a finding confirmed in the present study and contrary to the experience of Hoagland and associates,[1p] who regularly found a rise. Individual insulin treatments also had no consistent effect in the present study. However, when studies are made over a long period, definite trends appear. Lowering of the average output of 17-ketosteroids occurred in every instance in which there was decided clinical improvement. Improvement was considered by the clinical staff to have occurred in 1 patient (case Co, chart 6) who received electric shock, at a time when no lowering of excretion of 17-ketosteroids had occurred. It is possible that confusion consequent to electric shock was mistaken for improvement in the psychosis, for electric shock treatments were resumed a short time later and continued three times a week for another month, without improvement. Slight improvement was also considered to have occurred in another patient (case W, chart 2) during psychotherapy; she was a neurotic patient who lost some of her fears after several interviews. The patients who did not improve showed no decrease in excretion of 17-ketosteroids late in the course of treatment. Observations on the effect of a course of electric shock therapy on the output of 17-ketosteroids have been reported by other authors. Hemphill and associates,[5] who made single measurements before and again after a course of shock therapy, recorded no consistent change in output, although their 6 patients who did not improve showed no change at all. The use of isolated measurements in this manner does not yield valid data. Ashby [7] concluded that no consistent change in excretion of 17-ketosteroids occurred during the course of shock treatment; when, however, his data are plotted in accordance with the method used here, it appears that of 6 of his patients who were much improved, 4 showed a late fall in average output, while the 2 who were much improved, the 2 who were moderately improved and all who showed no improvement exhibited no change. The

9. Landau, R. L.; Knowlton, K.; Anderson, D.; Brandt, M. B., and Kenyon, A. T.: The Effect of Starvation on Urinary 17-Ketosteroid Excretion, J. Clin. Endocrinol. **8**:133, 1948.

10. Reiss, M.: Unusual Pituitary Activity in a Case of Anorexia Nervosa, J. Ment. Sc. **89**:270, 1943.

occurrence of a late fall in output of 17-ketosteroids in two thirds of the patients who were strikingly improved is remarkable in view of the initial low values, presumably consequent to severe malnutrition, found by this author. It is possible that the tendency to decreased output of these steroids which occurs with improvement was masked by the effects of an increase in caloric intake.

Seven of the patients showed an early increase in excretion of these substances during the course of treatment. The clinical records are not clear in every case, but it appears that this physiologic change is associated with agitation, excitement or hyperactivity; in 2 instances (cases F and Cu, charts 2 and 3) a striking increase in appetite occurred at the same time.

The good correlation between change in excretion of 17-ketosteroids and recovery from psychosis found in this study is in accord with a hypothesis relating psychosis to certain changes in adrenal cortex function.[11] However, measurement of excretion of 17-ketosteroids is far too laborious to make it valuable as a test for efficacy of psychiatric treatment, and interpretation of the findings is difficult when considerable changes in caloric intake occur. In addition, the urinary 17-ketosteroids include substances of diverse function and of no function; they are derived from the adrenal gland in both sexes and, in addition, from the gonads in men. Accordingly, no precise formulation can be made in physiologic terms of the nature of the changes noted here or of their significance in relation to psychosis, especially since no information is at hand as to which of the several steroid hormones measured together in the urine with the method used varied, and in which direction. Accordingly, in the present study, changes in output of 17-ketosteroids have been used only to obtain information as to whether shock treatment stimulates or depresses adrenocortical function in the long run.

It is of interest that in patients given electric shock treatments increases in excretion of 17-ketosteroids are likely to occur during an interval when decreases in lymphocyte and eosinophil counts and increases in urinary uric acid–creatinine ratios after each treatment are large; subsequently, when changes in these indexes of adrenocortical activity become smaller, to the point of insignificance, after electric shock treatments (charts 8, 9 and 10), the excretion of 17-ketosteroids is below normal. It should not be concluded that all of the adrenocortical functions are depressed at this time, for other work has shown that the doca® (desoxycorticosterone acetate)-like effects increase early and remain increased, although not above normal, thereafter.[12]

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11. Altschule, M. D.: Physiologic Observations in Mental Disease, Bull. New England M. Center **11**:229, 1949.

12. Altschule, Ascoli and Tillotson.[11] Altschule, Grunebaum and Promisel.[11a] Grunebaum and Altschule.[10]

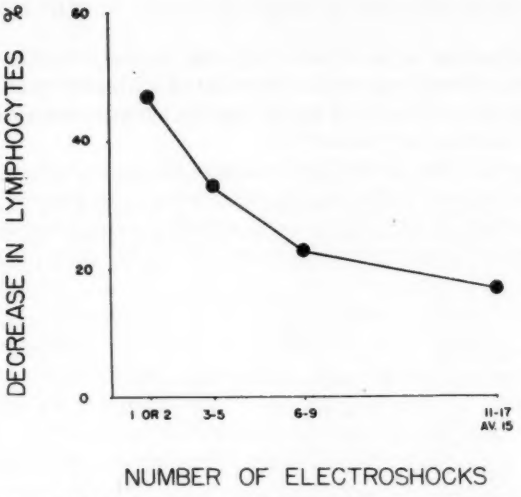

Chart 8.—Diminishing effect of electric shocks on lymphocyte count.

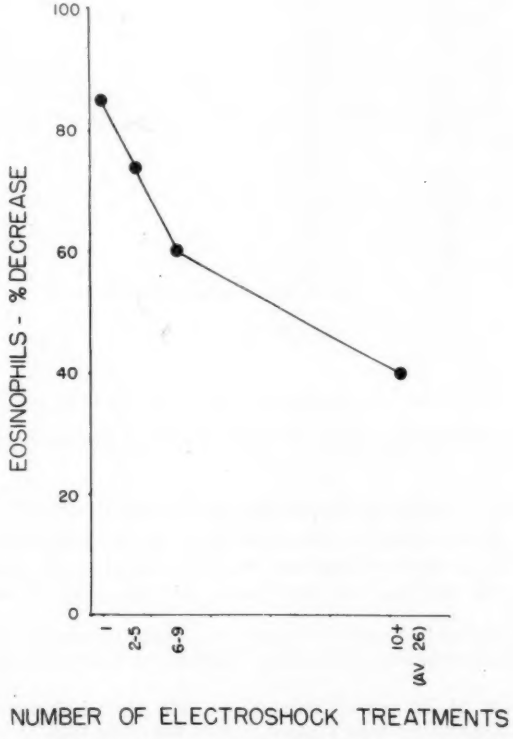

Chart 9.—Diminishing effect of electric shock on eosinophil count.

That 1 patient (case F, chart 2) who reacted strongly to psychotherapy also showed changes in excretion of 17-ketosteroids is not surprising; other work has also shown that the adrenal cortex is stimulated during psychiatric interviews.[13]

Of interest, also, is the fact that large amounts of progesterone did not depress adrenal cortex function in 3 severely ill patients (cases Co, S and H, chart 7) and, likewise, did not effect clinical benefit, although in patients with less severe psychoses steroid hormones may produce

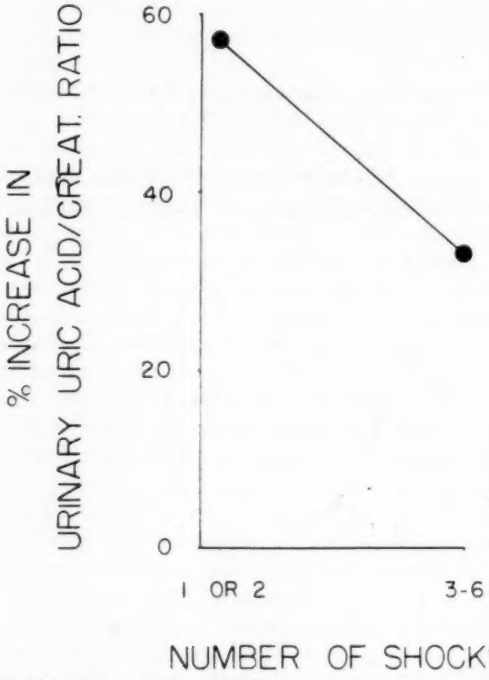

Chart 10.—Diminishing effect of electric shocks on urinary uric acid-creatinine ratio.

remission. In 1 patient of the present study (case R, chart 5) decreased output of 17-ketosteroids and remission of the psychosis occurred together after a course of electric shocks; several weeks later relapse began, but the injection of testosterone at this point[14] reversed the

13. Grunebaum and Altschule.[10] Shands, H. C., and Finesinger, J. E.: Lymphocytes in the Psychoneuroses: Preliminary Observations, Am. J. Psychiat. **105**:277, 1948.

14. Altschule, M. D., and Tillotson, K. J.: The Use of Testosterone in the Treatment of Depressions, New England J. Med. **239**:1036, 1948.

relapse. Possibly the steroid hormones, ineffective in depressing adrenocortical activity in severe psychosis, may have the effect of keeping the adrenal cortex depressed after this change has been secured with shock therapy.

SUMMARY AND CONCLUSIONS

The daily excretion of 17-ketosteroids is in or slightly above the normal range in patients with psychoses or severe neuroses. The values found are high if the reduced caloric intake of the patients is considered.

Early in the course of psychotherapy, insulin therapy or electric shock therapy increased excretion of 17-ketosteroids may occur. Late in the course of treatment, and after it, a dimunition in output is found in patients who show notable improvement, whereas no decrease occurs in patients who are not improved. These changes may be masked by an increase in excretion of 17-ketosteroids when an increase in caloric intake occurs in association with remission of the psychosis.

THE CEREBROSPINAL FLUID IN METHYL ALCOHOL POISONING

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THE EXISTENCE of cerebral edema and the therapeutic value of drainage of the cerebrospinal fluid in acute methyl alcohol poisoning have been recognized. The use of frequent lumbar puncture in treatment of this type of intoxication was first recommended in 1920 by Zethelius and Wersen and by Pincus.[1] In a series of 7 patients whom they treated with frequent lumbar punctures the visual capacity became normal in 4, while the remaining 3 had restoration of fairly good visual acuity. Other authors [2] have corroborated their results. Duursma and Huizinga [2b] cited a case from the clinic of psychiatry and neurology at Gröningen in which the spinal fluid was examined for methyl alcohol. The spinal fluid was found to contain methyl alcohol, and the patient's condition was improved after the first spinal tap. Duursma and Huizinga concluded that treatment must be aimed at removal of the toxin from the spinal fluid as early as possible. They claimed that this could be accomplished most conveniently by means of cisternal puncture. They added, however, that if the physician is not skilled in this procedure he may perform frequent lumbar punctures. The removal of as much as 50 to 70 cc. of spinal fluid was described.

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All cases were studied in the Neuropsychiatric Service of the United States Naval Hospital, Portsmouth, Va.

This article has been released by the Division of Publications of the Bureau of Medicine and Surgery of the United States Navy. The opinions and views set forth in this article are those of the writer and are not to be construed as reflecting the policies of the Navy Department.

1. Zethelius, M., and Wersen, A.: Behandlung der Methyl-Alkoholvergiftung, insbesondere der Sehstörung, mit Lumbalpunktion, Klin. Monatsbl. f. Augenh. **65**:51, 1920. Pincus, F.: Zur Behandlung der Methylalkohol-Erblindung mit Lumbalpunktion, ibid. **65**:695, 1920.

2. (*a*) Mathewson, G. H., and Alexander, B.: Blindness from Methyl Alcohol Successfully Treated by Lumbar Puncture, Canad. M. A. J. **26**:679, 1932. (*b*) Duursma, S. A., and Huizinga, T.: De behandeling van lijders aan methylalcoholintoxicatie, Nederl. tijdschr. v. geneesk. **91**:83 (Jan. 11) 1947.

More recent reports [3] have not emphasized the insidious character and frequency of increase in spinal fluid pressure which exists in this condition, nor have they noted the improvement in clinical status which follows the reduction of an increased pressure. Jacobson and associates [3b] performed lumbar punctures on 3 patients who were seen twenty-four to seventy-two hours after ingestion of methyl alcohol. They found that the initial pressure was elevated to 330 mm. of water in 1 patient, but the following day the pressure was recorded as normal. Autopsy in 6 of their cases indicated that unsuspected abnormal spinal fluid pressures were present oftener than recognized. They reported that the dura was tense in all cases. The pia-arachnoid was lifted above the convolutions by the accumulation of clear spinal fluid. There was herniation of the cerebellum into the foramen magnum. Sections of the brains revealed swelling and congestion throughout the cerebral hemispheres and the brain stem. In addition, there was notable engorgement of the vessels of the pia-arachnoid. The vessels of the ventricles were especially hyperemic, and small punctate hemorrhages could be discerned in scattered areas. Microscopic examination disclosed severe subpial edema with engorgement of the small cortical vessels, associated with extensive perivascular edema. Small focal areas of hemorrhage were seen in the cortex and the brain stem. Kaplan and Levreault [3c] reported a series of 42 patients seen twenty-four hours to a few days after ingestion of methyl alcohol. They recorded 6 cases of death after convulsive seizures of the decerebrate type, and 7 other cases of death in coma. They observed memory defects and mental confusion in all of a series of 13 patients whose symptoms were classified as moderately severe. Five of this group later passed into coma and died. The authors expressed the belief that methyl alcohol, formaldehyde and formic acid have a specific affinity for the central nervous system, optic nerve, respiratory center and vagus nerve. They stated that the clinical picture was one of accumulating injury to the nervous system.

In this report is emphasized the indication for repeated spinal punctures for the removal of excessive spinal fluid and the reduction of increased pressure, so often observed. As far as is known, an elevation of cerebrospinal fluid pressure persisting over a five week period has not previously been recorded.

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3. (*a*) Merritt, W. A., and Brown, A. E.: Methyl Alcohol Poisoning: Report of a Case, Proc. Staff Meet., Mayo Clin. **16**:666 (Oct. 15) 1941. (*b*) Jacobson, B. M.; Russell, H. K.: Grimm, J. J., and Fox, E. C.: Acute Methyl Alcohol Poisoning: Report of Eighteen Cases, U. S. Nav. M. Bull. **44**:1099, 1945. (*c*) Kaplan, A., and Levreault, G. V.: Methyl Alcohol Poisoning: Report of Forty-Two Cases, ibid. **44**:1107, 1945. (*d*) Chew, W. B.; Berger, E. H.; Brines, O. A., and Capron, M. J.: Alkali Treatment of Methyl Alcohol Poisoning, J. A. M. A. **130**:61 (Jan. 12) 1946.

PROCEDURE

Approximately twenty hours after their admission to the hospital 10 of the total 23 patients showing the most conspicuous clinical evidence of methyl alcohol intoxication had spinal punctures. These initial taps were made with special attention to the avoidance of errors in determining spinal fluid pressures. The patients were reassured and put at as much ease as the situation would permit. The cranium and spinal canal were placed in horizontal alinement. Abnormal flexion of the head on the thorax was avoided. Routine lumbar entries were made with the use of standard hospital spinal tray preparations. Before the pressures were read, sufficient time was allowed to permit stabilization of the fluid column in the manometer. The immediate, and most conspicuous, observation in 8 of the first 10 spinal punctures, performed approximately twenty hours after the patient's admission, was elevated pressure, as revealed by the manometric reading (see "Observations"). A reading of 150 mm. of water was taken as a recognized, but arbitrary, upper limit for the normal spinal fluid pressure. In all instances the fluid was crystal clear, and when the pressure was elevated it was reduced to within normal limits after drainage. Differential cell counts were made immediately. There was never more than 1 lymphocyte per cubic millimeter of fluid. The erythrocyte count ranged from zero to 10 cells per cubic millimeter. Determinations of the protein and glucose contents of the spinal fluid disclosed normal levels. The Kahn reactions, the colloidal gold curves and the differential cell counts were normal on the fifth and twelfth hospital days for 5 patients with definite ophthalmoscopic and clinical evidence of toxic reactions. Twelve patients had spinal punctures every one to two days during the first week of admission. During the second week 10 had spinal punctures on two occasions, at intervals of two to four days. No spinal punctures were done during the third week; however, in the fourth and fifth weeks 8 and 11 patients, respectively, had a single spinal puncture. Manometric readings of the spinal fluid pressure were taken in all instances.

The poisonous fluid consumed by the patients had been diluted with fruit juices. It was subjected to chemical analysis by a reliable laboratory, and the results were reported as follows:

Methyl alcohol, % by volume	98.8
Acidity as acetic acid	0.001
Aldehydes	Trace
Kerosenes	None detected
Gasoline	None detected
Mercaptans	None detected
Lead, as lead acetate, % weight per volume	0.05

OBSERVATIONS

For 4 patients of this group the termination was fatal. They passed into coma, and 3 of the 4 exhibited two to three generalized convulsions, predominantly tonic in character and persisting for several minutes. The occurrence of coma followed by convulsive episodes is generally recognized as occurring in methyl alcohol poisoning which ends fatally. The clinical status and treatment in the 4 fatal cases are summarized.

Case 1.—A white youth aged 18 was admitted to the medical dispensary *in extremis*, after having ingested an estimated twenty-four hours or more previously a substance presumed to be methyl alcohol. He was reported to have been vomiting the entire preceding day. On his admission to the dispensary his respirations were labored, with a rate of 30 per minute. The muscles were rigid. There was evi-

dence of slight cyanosis, but the pulse was regular. There was an odor of alcohol on the breath, and the reading in Bogan's test for blood alcohol was 5 mg. per cubic centimeter. The patient had been observed to have three generalized convulsions. Despite the usual emergency therapeutic procedures, the pulse and respirations gradually decreased in rate. He died within an hour after initiation of medical treatment, and autopsy was subsequently performed.

Case 2.—A white youth aged 18 was admitted to the hospital after having allegedly ingested a mixture of fruit juice and a fluid tentatively identified as methyl alcohol. Physical examination on admission disclosed a semicomatose patient who showed jactitation and thrashed his limbs about. During the examination he had a tonic convulsion which lasted about two minutes. The pulse was weak and irregular in quality, with a rate of 58 per minute. Heart sounds were described as faint, and the blood pressure was 90 systolic and 50 diastolic. The skin and mucous membranes were cyanotic. The respiratory rate was 10 per minute. The pupils were greatly dilated, regular and equal. The light reflexes and corneal reflexes were absent. The breath was described as smelling "ammoniacal." A stomach tube was passed to remove any possible residual of the poison, and the stomach was lavaged with a 4 per cent sodium bicarbonate solution. The stomach was then filled with the solution and the tube withdrawn. An intravenous transfusion of one-sixth molar sodium lactate solution was started. During the administration of fluids he had an additional tonic convulsion of approximately two minutes' duration, followed by a decrease in respiratory rate and by cyanosis. Inhalation of oxygen by mask was begun, and additional intravenous administration of fluids and plasma was initiated. The respirations ceased, and artificial respiration was unavailing. The heart sounds decreased in intensity, and the blood pressure could not be ascertained. Nikethamide and caffeine were administered, and artificial respiration was continued. All emergency measures were without apparent benefit. Approximately three and one-fourth hours after admission the patient was dead.

Case 3.—A white man aged 24 was brought to the hospital after an illness of twenty hours. He was alleged to have drunk fluid tentatively identified as methyl alcohol an estimated minimum of twenty-four hours prior to his admission to the hospital. Physical examination on admission revealed him to be in light coma, with pupils dilated and not reactive to light. The corneal reflexes were present. The deep reflexes were absent, but he reacted to strong pain stimuli. The blood pressure was 100 systolic and 65 diastolic. The pulse was irregular and weak, with a rate of 20. The heart sounds were faint and irregular. The respirations were irregular, with a rate of 11 per minute. There was a sweetish odor to the breath. Immediately after his admission the stomach was emptied by tube and irrigated with 4 per cent sodium bicarbonate solution. The tube was withdrawn, and some of the solution was left in the stomach. The patient was given 1,500 cc. of one-sixth molar sodium lactate solution intravenously, followed by injection, over the hospital period, of 1,000 cc. of 5 per cent dextrose in isotonic sodium chloride solution and 1,000 cc. of plasma. Caffeine was given in a dose of 0.5 Gm. every two hours. Oxygen inhalations by mask were instituted. Six and one-half hours after his admission the respirations were noted to be deep and irregular, with a rate of 14 per minute. The pulse was strong and regular, with a rate of 100 per minute. The blood pressure was 128 systolic and 80 diastolic. The corneal reflexes were absent. The neurologic status showed no improvement. Despite treatment, coma became deeper, and breathing was described as Kussmaul in type. Artificial respiration and the repeated administration of nikethamide and caffeine failed to effect improvement. The patient died eight and one-half hours after admission.

Case 4.—A Negro aged 19 stated that about twenty-three hours before admission he drank a mixture of orange juice and a fluid that was allegedly used for testing leaks in refrigeration systems. The fluid was tentatively identified as methyl alcohol. The patient said he had consumed "just a sip" and was reported to be feeling well on the day of admission to the hospital. He was not observed to have any objective or subjective complaints. Physical examination on admission showed a well developed well nourished person who appeared anxious but had no evidence of physical distress. Otherwise, the condition was reported to be essentially normal. He received a solution of sodium bicarbonate by mouth and was then given a mildly emetic dose of 3 mg. of apomorphine hydrochloride hypodermically. He complained of gastric distress following this measure. Then, after emesis, he was given intravenously 500 cc. of a one-sixth molar solution of sodium lactate and 1,000 cc. of 5 per cent dextrose in isotonic sodium chloride solution. He responded well, and at 8:30 the following morning, fourteen and one-half hours after admission, he complained of being hungry but had no other complaint. At approximately 11:00 a. m. he was noted to be cold and clammy, but the pulse was still strong and the blood pressure 160 systolic and 110 diastolic. He was restless and disoriented and complained of abdominal cramps. He became

Spinal Fluid Pressures, in Millimeters of Water

	Pressure, Mm. of Water	Week After Ingestion			
		1	2	4	5
Extreme elevation	300-400	2	0	0	0
Definite elevation	200-299	9	8	5	5
Uncertain elevation	150-199	10	2	3	3
Normal pressure	0-149	10	4	0	3
No. of patients	.....	12	10	8	11
No. of spinal taps	.....	31	14	8	11

delirious and was given 4 cc. of paraldehyde intramuscularly to control jactitation. He soon became comatose, and respirations were deep and irregular. The blood pressure and pulse were maintained. He was given inhalations of oxygen and stimulants, including epinephrine, nikethamide and aminophylline. Although the pulse and blood pressure remained unchanged to the end, respirations became slower and finally ceased approximately twenty hours after his admission. Shortly preceding his death he was observed to have repeated generalized tonic convulsions. He died before a spinal puncture was done.

Comment.—The clinical and neurologic responses in these 4 cases were strongly suggestive of the occurrence of acute cerebral edema as the basis for the neurologic changes.

After the death of the last patient, study of the spinal fluid of 10 patients who had ingested methyl alcohol was begun. The significant abnormal feature of these spinal fluids was the increased pressure. The initial pressures, in millimeters of water, were as follows: 390, 300, 252, 230, 220, 180, 170, 150, 140 and 120. Patients with the lowest initial pressures showed the following subsequent increases: The 120 mm. pressure rose in two days to 240 mm.; the 140 mm. pressure, in ten days to 206 mm. and the 150 mm. pressure, the next day to 190 mm. The findings for this series are summarized in the accompanying table.

It can be determined from this table that extreme increases occurred only in the first week. Definite elevations of cerebrospinal fluid pressure were sustained through a five week period. Forty-five per cent of the spinal punctures performed showed pressures of 200 mm. of water or above. These elevations persisted five weeks after admission in 8 of 11 patients who had shown notable improvement of their retinal lesions. These pressures, in millimeters of water, were 220 mm. (2 patients), 210 mm. (2 patients), 200, 180 and 170 mm. (2 patients). The remaining 3 patients had pressures lower than 150 mm. The spinal fluid pressures of the fourth week were somewhat higher than but were otherwise comparable, patient for patient, to those of the fifth week. It was not clinically possible to detect the presence of abnormal spinal fluid pressures, and after evaluation of the data no significant relation could be established.

The patient with the severest ophthalmoscopic changes and visual impairment had an average spinal fluid pressure of 145 mm. on four occasions during the first week, his highest pressure being 190 mm. on the third hospital day. Another patient had a pressure of 230 mm., with little ophthalmoscopic or other evidence of a toxic effect. Six of the 10 patients who had spinal punctures on the second hospital day showed ocular changes associated, but not correlated, with the degree of pressure. After these spinal punctures there were no additional occurrences of coma, convulsions or death. It was the opinion of the physicians attending these patients that the initial drainages of spinal fluid performed during the first three days were life saving in several cases in which life was threatened and in which the cerebrospinal fluid was elevated. It was noted at the time, as well as in retrospect, that there were no signs indicating elevated pressure of the spinal fluid other than those obtained by direct measurement. The ophthalmologist, Dr. D. Hoxie, was aware of striking improvement in the ocular fundi, as well as in responses to both visual and color field tests in the cases observed in this series.

The beneficial effect of spinal drainage used simultaneously with the therapeutic procedures for combating acidosis resulted in improvement in confusion and mental dulling. Cardiac palpitations, substernal oppression and apprehensive sensations, most probably of toxic rather than psychic origin, subsided. One patient, who showed minimal clinical evidence of intoxication, suddenly manifested characteristic symptoms with papilledema approximately three days and six hours after consuming the methyl alcohol. The spinal fluid pressure was found elevated to 235 mm. of water and then reduced to within normal limits. He received contemporaneously standard supportive medical treatment for acidosis. He showed prompt improvement the next day and subsequently remained asymptomatic. The value of performing spinal taps

cannot be conclusively determined from these cases, but when spinal puncture is performed early as an adjuvant to systemic therapy it appears to be a lifesaving procedure.

Two patients were chosen for detailed neurologic examination on the third hospital day, which was approximately seventy-two hours after ingestion of the methyl alcohol. One was chosen for examination because he demonstrated the severest objective and subjective visual impairment. The cerebrospinal fluid had no increase in cells, and the spinal fluid pressure was not elevated at the time of examination. The second was chosen because the available history disclosed him to have consumed the largest quantities of the methyl alcohol. He also showed the highest cerebrospinal fluid pressure of 390 mm. of water, twenty hours after admission, and had characteristic papilledema with inflammatory cells in the spinal fluid.

Case A.—Neurologic examination revealed a white youth lying in bed, responsive and cooperative. He was noticeably apprehensive but showed little evidence of physical distress. He complained of the room being dark and asked whether the lights were on. He displayed, and was aware of, mental confusion. Although he had a tenth grade education, he performed simple calculations poorly. The 100—7 subtraction test was done erratically. When asked to smell a sponge with ethyl alcohol, he commented, without speech difficulty, "I never smelled anything like that before." When told to walk, he complained of being "light headed." His gait was unsteady and characterized only by its broad base. The blood pressure was 140 systolic and 48 diastolic. He was unable to see the examiner's fingers with the left eye when they were held 1 foot (30 cm.) from it in daylight; with the right eye he had difficulty in determining the number of fingers presented. The pupils were round and symmetric and reacted normally to light. Pain was experienced on palpation of the orbs. No abnormal turgor was detected. Ophthalmoscopic examination of the fundus was accomplished at 0 D. in each eye. The optic disk of the right eye was noticeably edematous and elevated. There was an area of peripheral gray pallor of the retina, adjacent and temporal to the optic disk, and hyperemia was not detected at this time. The left eye had a comparable distribution of the ischemic grayish pallor, which was somewhat severer. No nystagmus could be elicited. Deep reflexes were equally and symmetrically present, but the knee jerks were elicited only with reenforcement. The plantar responses were flexor. Twenty hours preceding this examination the patient was observed to have had a strikingly positive Babinski sign with positive confirmatory signs on the left. The Babinski sign was never observed on the right and had disappeared completely at the time of this examination. Cranial nerves, except for the optic nerves, gave normal responses. Tests of strength gave normal results. No abnormal tone was detected in the muscles. Abdominal skin and cremasteric reflexes were normal. Temperature, vibration, light touch and pinprick sensations were perceived and reacted to normally. Meningeal signs were absent.

Case B.—A young white man showed continued evidence of moderate alcoholic intoxication but displayed no euphoria. He was mildly apprehensive and demonstrated confusion. He was unable to state the month and date correctly. The 100—7 subtraction test was done poorly, although he had a seventh grade education. He was unable to repeat four spoken numbers in reverse order. He followed simple directions in a slow, confused, erratic manner. A thick, sluggish speech,

similar to that of ethyl alcohol intoxication, was observed. Test phrases were clumsily spoken. The blood pressure was 128 systolic and 68 diastolic. He complained of "a pounding heart." No cardiac irregularities could be ascertained from the clinical examination. Deviation of the eyes laterally elicited a complaint of pain and slight nystagmus. No pain was present on palpation of the eyes, nor was there abnormal turgor. The pupils reacted to light and were equal, round and symmetric. The fundi were visualized at 0 D. The margins of the optic disks were edematous, and both retinas were hyperemic. No gross impairment of vision was detected. The knee jerks were obtained only with reenforcement. Otherwise, routine neurologic tests revealed an essentially normal status.

The sensorial defects, observed at the time of these examinations, were in progress of subsidence and disappeared slowly during the forty-eight hours following examination. The mental confusion and memory defects of intoxication observed in these 2 patients were generally recognized to be present in varying degrees in all those patients who exhibited the abdominal cramps, visual defects, blurred vision and headache characteristic of this type of intoxication.

CONCLUSIONS

Sixty-four spinal punctures were performed on 13 patients with acute methyl alcohol poisoning. Abnormal elevation of spinal fluid pressure occurred in 5 of 11 patients throughout a five week period of convalescence.

In 8 of 10 patients spinal puncture performed on the third day after ingestion of the poison showed elevated pressures. Two had pressures of 300 and 390 mm. of water, respectively; 3, a pressure of over 200 mm. of water, and 3, pressures of over 150 mm. of water.

All patients known or suspected of having ingested methyl alcohol should have repeated determinations of the spinal fluid pressure during the week following ingestion, in addition to the accepted standard procedures. Elevated pressures should be reduced by drainage. By this procedure, toxic metabolic products may be removed.

It is not possible to determine from clinical findings in the conscious patient the presence of an increased cerebrospinal fluid pressure. Direct manometric measurement is therefore indicated to determine the spinal fluid pressure in all suspected cases. This procedure was judged to be an important emergency and therapeutic measure.

Death apparently occurs as a result of accumulative toxic products. The effects of abnormal cerebrospinal fluid pressure on the central nervous system are reflected in delirium, coma, convulsions and central respiratory depression, in the presence of acidosis.

Generally, patients with the most obvious ophthalmoscopic changes also had abnormally high spinal fluid pressures.

TETRAETHYLAMMONIUM CHLORIDE IN THE TREATMENT OF MULTIPLE SCLEROSIS

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OUR INTEREST in tetraethylammonium chloride was aroused quite by accident in August 1947. Tetraethylammonium chloride was used in an effort to relieve an intense causalgic state which had followed bilateral alcohol injection of the posterior tibial nerves in a case of multiple sclerosis with severe spasm of the plantar flexors of the feet. About two weeks after the beginning of therapy remarkable resolution of the long-standing paraplegia began. So dramatic was the improvement that an investigation of the possible role of tetraethylammonium chloride was considered necessary. Similarly suggestive results obtained in a second case of the disease treated shortly thereafter led us to undertake a more thorough evaluation of the drug in management of multiple sclerosis.

Further impetus was given to the continuation of the study by the report of Bell, Williams and Karnosh.[1] These workers found a favorable response in 14 acute cases and unfavorable results in 8 cases of long-standing multiple sclerosis treated with tetraethylammonium chloride. It was their impression that continued treatment protected against relapse and progression in early cases. Later, in September 1949, in a general discussion of multiple sclerosis, Williams and Bell[2] mentioned treating 300 patients with tetraethylammonium chloride, given six times weekly for several months, with equivocal conclusions. They claimed that "a majority of the patients with an acute relapse apparently begin definite

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1. Bell, E.; Williams, G. H., and Karnosh, L. J.: Tetraethylammonium Chloride in Multiple Sclerosis, Cleveland Clin. Quart. **15**:90, 1948.

2. Williams, G. H., and Bell, E.: Present Day Status of Multiple Sclerosis, Mississippi Doctor **27**:130, 1949.

improvement within three to five days after the start of treatment." It was further stated that relapses were neither completely cleared nor entirely prevented by the drug but that its administration produced a "definite and beneficial effect" in most cases of the disease. It had no effect on the steadily progressive forms of the disease.

The theoretic considerations behind the possible value of such a drug stem from the concept that multiple sclerosis may have a vascular origin. Franklin and Brickner [3] postulated that vasospasm on an allergic or a toxic basis may be responsible for the foci of disease. Putnam and associates,[4] in their study of dicumarol® in the treatment of multiple sclerosis, recently reviewed the theory that thrombosis occurring in venules is an essential link in the causation.

NATURE OF THE DRUG

Tetraethylammonium chloride is a stable quaternary ammonium compound which blocks reversibly both sympathetic and parasympathetic impulses at the ganglia.[5] These effects are antagonized by acetylcholine and epinephrine, which act peripheral to the ganglia. Because of its ability to produce vasodilation, the drug has been used widely in man in the diagnosis and treatment of occlusive peripheral vascular disease, reflex dystrophy, Raynaud's phenomenon, trench foot, immersion foot, causalgic states and hypertension.[6]

Tetraethylammonium chloride may be given intravenously in doses not exceeding 7 mg. per kilogram of body weight. The chief side effects which we have noted to follow intravenous injection included tachycardia, paresthesias of the extremities, dryness of the mouth, a feeling of generalized warmth, blurring of vision, lightheadedness and, at times, a precipitous fall of blood pressure. All these effects disappeared within three to ten minutes after intravenous injection. Caution must be

3. Franklin, C. R., and Brickner, R. M.: Vasospasm Associated with Multiple Sclerosis, Arch. Neurol. & Psychiat. **58**:125 (Aug.) 1947.

4. Putnam, T. J.; Chiavacci, L. V.; Hoff, H., and Weitzen, H. G.: Results of Treatment of Multiple Sclerosis with Dicoumarin, Arch. Neurol. & Psychiat. **57**:1 (Jan.) 1947.

5. Lyons, R. H., and others: The Effects of Blockade of the Autonomic Ganglia in Man with Tetraethylammonium Chloride, Am. J. M. Sc. **213**:315, 1947.

6. Coller, F. A., and others: Tetra-Ethyl-Ammonium Chloride as an Adjunct in the Treatment of Peripheral Vascular Disease and Other Painful States, Ann. Surg. **125**:729, 1947. Lyons, R. H., and others: Experiences with Tetraethylammonium Chloride in Hypertension, J. A. M. A. **136**:608 (Feb. 28) 1948. Yeager, R. H.; Walker, J. H., and Raby, W. T.: Clinical Evaluation of Tetraethylammonium, South. M. J. **41**:129, 1948.

observed in the intravenous use of the drug, for on occasion 100 mg. of tetraethylammonium chloride may cause a fall of blood pressure to shock levels in adults with normal blood pressure. The maximum toxic effect after intramuscular injection, noted in thirty to sixty minutes, included blurring of vision (paralysis of accommodation with preservation of the pupillary response to light), a feeling of generalized weakness, dryness of the mouth, tachycardia and postural hypotension. The last-mentioned effect was so frequently encountered that all patients were kept in the recumbent attitude for one hour after intramuscular injection. In patients maintained for weeks on intramuscular doses just below the amount causing blurring of vision, changes in blood pressure were negligible except for the previously noted transient postural hypotension. However, such patients frequently complained of pronounced lassitude and generalized weakness, which required downward modification of the dose. A tendency to constipation and difficulty in starting the urinary stream were also frequently encountered. These effects are consistent with decreases in intestinal motility [7] and vesical tone [8] described in the literature.

METHOD OF TREATMENT

Since there was no way of anticipating what to expect, it was decided to treat patients intensively for a short time in the hospital and to follow this with less frequent treatment at home. All patients were hospitalized for three weeks. Each was given an intravenous test dose of 100 to 350 mg. of tetraethylammonium chloride initially to determine any unusual response to the drug. In no case was such a response encountered. After this, treatment consisted of deep intramuscular injections of tetraethylammonium chloride into the buttocks three times daily. Total daily doses averaged 1,200 mg. and ranged from 300 to 1,800 mg. When the patient was discharged from the hospital, members of the families were taught to give the injections at home, and the usual doses were from 200 to 400 mg., two to four times a week. The level of continued treatment was dependent on the patient's reactions with regard to lassitude, fatigue or blurring of vision.

All the patients were examined completely prior to treatment and at intervals thereafter as often as possible. Complete records of the neurologic examinations were made and saved for analysis at a later date.

ANALYSIS OF MATERIAL

Our material consisted of 42 patients with an unequivocal diagnosis of multiple sclerosis. Many of these had had previous diagnosis and had been treated at clinics in various parts of the country. All of them were treated with

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7. Neligh, R. B., and others: The Effect of Blockade of Autonomic Ganglia by Tetraethylammonium Chloride in the Gastrointestinal Tract in Man, Proc. Am. Federation Clin. Research. **3**:20, 1947.

8. Nesbit, R. M., and others: The Effects of Blockade of the Autonomic Ganglia on the Urinary Bladder in Man, J. Urol. **57**:242, 1947.

tetraethylammonium chloride for a period of three weeks in the hospital. Nineteen were not available for examination after discharge. On some of the latter follow-up reports were obtained from their physicians or by letter from the patients themselves. The remaining 23 patients were personally followed for from three to thirty months. For purposes of orientation, we may describe our cases as follows: Six patients had persistent paraplegia; 13 had severe enough disorders that they could get about only with great help, and then to a limited degree, and the remaining 23 patients were sufficiently ambulatory to work or to take care of their household obligations fairly well.

The effect of any treatment in a disease such as multiple sclerosis is difficult to establish. Some investigators have been content to use subjective statements as criteria of improvement, but such conclusions are notoriously unreliable.[9] They are often dependent on the psychogenic effect of the relationship between a chronically disabled patient and a sympathetic physician, as suggested in a report by Langworthy.[10] The observation that acute episodes improve with a particular treatment cannot be accepted as a valid test of therapy, for spontaneous remission in these states is well known.[2]

Another method has been used by Putnam and associates [2] in an effort to study statistically the effect of treatment in preventing the progress of the disease, it being assumed that persistent signs of damage to the nervous system could not be expected to disappear since they were the results of irreversible disease. This was done by showing that the expected rate of relapse for series of patients was such that some patients should have had exacerbations in the treatment period, as estimated from their previous performance. The fact that they did not was accepted as evidence of the efficacy of treatment with dicumarol. The hazard of such a conclusion in a small series followed even for a few years is obvious. This is made even more apparent by the patients with chronic progressive disease who continued to grow worse under treatment.

It is our belief that one can evaluate the efficacy of treatment only on objective grounds. It must be shown that the treatment will either cause resolution of existing signs or prevent the occurrence of new pathologic changes. If only gross episodes of the disease were to constitute progression, a very large series of cases would have to be studied for a long time. On the other hand, careful study of a relatively small heterogeneous series of cases can provide a means of determining whether objective signs of progression appear in the cases of chronic progressive disease, or even in the cases of remitting type, in which gross episodes of paralysis, ataxia etc., do not occur.

METHOD OF ANALYSIS

In order to analyze objectively the progress in each case, we chose for specific study certain constant, easily followed criteria of the neurologic examination. These were augmented by the observation of unusual signs or symptoms in any individual

9. Putnam, T. J.: The Criteria of Effective Treatment in Multiple Sclerosis, J. A. M. A. **112**:2488 (June 17) 1939.

10. Langworthy, O. R.: Relation of Personality Problems to Onset and Progress of Multiple Sclerosis, Arch. Neurol. & Psychiat. **59**:13 (Jan.) 1948.

case. In addition, statements of the subjective status were recorded. In the following tabulation are indicated the neurologic criteria and the grading ascribed to them in accordance with the severity of disturbance at the time of examination.

1. Gait
   5 Normal
   4 Disordered gait without support
   3 Support of cane needed
   2 Constant and bilateral support or support of attendant needed
   1 Patient bedridden

2. Strength
   5 Normal
   4 Movement against resistance
   3 Movement against gravity
   2 Movement without gravity
   1 No movement

3. Tone

   Hypertonus
   3 Normal
   2 Mildly hypertonic
   1 Spastic

   Hypotonus
   3 Normal
   2 Mildly hypotonic
   1 Flaccid

4. Stance
   3 Normal
   2 Moderate disturbance
   1 Inability to stand with feet together

5. Cerebellar Signs (intention tremor)
   3 Normal
   2 Mild
   1 Severe

6. Muscle Stretch Reflexes

   Hyperactive
   3 Normal
   2 Exaggerated
   1 Spastic

   Hypoactive
   3 Normal
   2 Decreased
   1 Absent

7. Abdominal Reflexes
   3 Normal
   2 Diminished (some absent or diminished)
   1 Absent

8. Clonus
   3 Absent
   2 Exhaustible
   1 Inexhaustible

9. Hoffmann Sign
   3 Absent
   2 Unilateral or inconsistent
   1 Bilateral

10. Babinski Sign
    3 Absent
    2 Unilateral or inconsistent
    1 Bilateral

11. Position Sense
    3 Normal
    2 Impaired
    1 Absent

12. Vibration Sense
    3 Normal
    2 Impaired
    1 Absent

13. Perception of Pinprick
    3 Normal
    2 Impaired
    1 Absent

14. Perception of Cotton
    3 Normal
    2 Impaired
    1 Absent

15. Nystagmus
    3 Normal
    2 Inconstant
    1 Constant

16. Optic Disks
    3 Normal
    2 Some atrophy
    1 Pronounced atrophy

17. Speech
    3 Normal
    2 Mild impairment
    1 Severe impairment

18. Bladder Status
    3 Normal
    2 Control with urgency or delay
    1 Incontinence

The recorded examinations for each patient were reviewed simultaneously, and each component was graded according to the foregoing standards. The results of the first examination were considered the patient's base of disability. Any change from this (improvement or regression) was indicated by altering the grade initially ascribed. If minor changes were noted, they were recorded as plus or minus. This method, however crude, enabled us to tabulate a concise and realistic summary of each patient's course. When the data were reviewed at one sitting, we could get an objective concept of the course of the illness without being influenced by the patient's subjective responses. The results could then be charted, as is shown in the following illustrative case:

M. L. D., a white woman aged 38, became ill three months before coming under our observation She had noted numbness of the left thigh and perianal region for three months and had suffered unsteadiness of gait and dizziness associated with vomiting for two months.

By following across the chart the numbers recorded for any one neurologic criterion, one is easily aware of what happens in that particular category. Thus, it is apparent that a mildly disturbed gait returned to normal. The strength was normal at the beginning and the end of our observation period, but in the interim there developed paresis of the right upper extremity, which recovered quickly.

Stance and bladder control were normal at first and became disturbed for a short time only. She had a mild intention tremor in both upper extremities; this disappeared from one arm. The abdominal reflexes, which were easily exhausted at first, disappeared for a while and then returned feebly. A bilateral Hoffmann sign appeared temporarily after two months of treatment. Perception of cotton was decreased over one lower extremity but returned to normal. There was an obvious nystagmus, which disappeared after four months, only to reappear two months later. All other categories were normal. The patient's subjective status was greatly improved because of the disappearance of dizziness and paresis of the right upper extremity.

RESULTS

Each case was analyzed in the manner described. The results of tetraethylammonium chloride therapy were then summarized for two

TABLE 1.—*Individual Patient Analysis Chart*

Diagnostic Criteria	7/10/49*	7/28	8/1	8/5†	9/8	10/14	11/22‡	1/12/50
Gait	4+	4+	4+	4+	5	5	5	5
Strength	5	4	4+	4+	5	5	5	5
Tone	3	3	3	3	3	3	3	3
Stance	3	2	2	3	3	3	3	3
Cerebellar signs	2	2	2	2	2+	2+	2+	2+
Stretch reflexes	2	2	2	2	2	2	2	2
Abdominal reflexes	2	2	2	1	1	1	1	2
Clonus	3	3	3	3	3	3	3	3
Hoffmann sign	3	3	3	3	2	1	3	3
Babinski sign	3	3	3	3	3	3	3	3
Position sense	3	3	3	3	3	3	3	3
Vibration sense	3	3	3	3	3	3	3	3
Perception of pinprick	3	3	3	3	3	3	3	3
Perception of cotton	2	2	2	2	3	3	3	3
Nystagmus	1	1	1	1	1	2	3	2
Optic disks	3	3	3	3	3	3	3	3
Speech	3	3	3	3	3	3	3	3
Bladder status	3	3	2	3	3	3	3	3

* Tetraethylammonium chloride started July 15.
† Tetraethylammonium chloride, 2 cc. three times a week, started on August 5.
‡ Tetraethylammonium chloride, 2 cc. twice a week, started on November 22.

groups of patients: (*a*) patients receiving intensive hospital treatment for three weeks, and (*b*) patients under long-term follow-up observation.

In order to avoid the difficult problem of evaluating results in individual cases, it was considered feasible to study the sum of all the pathologic signs in all patients. This gives a picture of the total amount of "pathology" among our patients and permits us to draw a base line from which improvement or regression can be measured. Each of the eighteen criteria in our neurologic examination was analyzed in terms of frequency of occurrence, instances of improvement or regression, appearance of changes not present in the initial examination and number showing no change. Thus, we could determine what proportion of pathologic signs present at the beginning of treatment showed improve-

ment, as compared with the total of those signs which regressed and signs which appeared during the course of treatment.

Analysis After Three Weeks of Treatment in Hospital.—All 42 patients were included in this group to determine any immediate effect of treatment. These patients presented 466 pathologic signs at the onset of treatment (table 2). At the end of three weeks of intensive treatment a total of 69 signs of improvement had appeared. These were scattered among 32 patients; it is evident therefore that the bulk of the changes were not accounted for by a small group of patients with a remitting type of disease. In contrast, there were 21 signs of regression. On the

TABLE 2.—*Three Weeks Therapy (42 Cases)*

Criteria	No. Showing Pathologic Sign	No. Showing Improvement	No. Showing Regression	No. Showing New Sign	No. Showing No Change
Gait	39	7	1	0	31
Strength	28	8	4	1	16
Tone	30	2	0	1	28
Stance	27	4	0	2	23
Cerebellar signs	33	9	2	1	22
Stretch reflexes	41	0	0	0	41
Abdominal reflexes	42	3	2	0	37
Clonus	34	7	4	2	23
Hoffmann sign	21	3	4	3	14
Babinski sign	37	3	1	1	33
Position sense	17	2	1	2	14
Vibration sense	17	8	1	1	8
Pin perception	3	1	0	0	2
Cotton perception	10	3	0	1	7
Nystagmus	30	4	1	1	25
Optic disks	15	0	0	0	15
Speech	8	0	0	1	8
Bladder status	34	5	0	1	29
Totals	466	69	21	18	376
Subjective status		23	1		18

surface, this difference would appear to be significant; at the same time, however, there was the appearance of 18 new pathologic signs, making a total of 39 signs of regression, scattered among 20 patients. Of the 69 signs of improvement, 39 were accounted for by changes in five criteria, namely, gait, strength, cerebellar signs, clonus and vibratory sense. It is known that gait and strength may improve with three weeks of relative bed rest, and it is probable that this could affect cerebellar signs and clonus. It is notable also that 17 of the 39 instances of regression and newly appearing signs occurred among the same five criteria. There was regression of strength in 5 patients (8 showed improvement); cerebellar signs became worse in 3 patients (9 showed improvement), and clonus became worse in 6 patients (7 showed improvement). It is noteworthy that the great bulk of the pathologic signs showed no changes at all.

Analysis of Long Term Treatment.—This group consisted of 23 of the original 42 patients. Seven were observed for three months; 6, for three to twelve months; 5, for twelve to eighteen months; 4, for eighteen to twenty-four months and 1, for thirty months. All these patients had what has previously been described as a maintenance dose of tetraethylammonium chloride.

In these patients the results of the initial examination were compared with those of the last examination while the patient was under treatment (table 3). There were 265 pathologic signs at the onset of treatment; 160 signs showed no change. There was improvement in 66 signs, scattered among 21 patients. In contrast to this, there were 39 signs of regression and 19 instances in which signs appeared which had not previously been present, making an actual total of 58 signs of regression among 18 patients. Thus, the impression from the 66 signs of improvement that tetraethylammonium chloride might have had a specific therapeutic effect is negated by the fact that at the same time there were 58 signs of regression.

TABLE 3.—*Long-Term Therapy (23 Cases)*

Criteria	No. Showing Pathologic Sign	No. Showing Improvement	No. Showing Regression	No. Showing New Sign	No. Showing No Change
Gait	21	4	3	1	14
Strength	15	3	4	1	8
Tone	14	3	5	4	6
Stance	16	5	3	1	8
Cerebellar signs	19	8	4	3	7
Muscle stretch reflexes	22	1	1	0	20
Abdominal reflexes	23	3	1	0	19
Clonus	21	6	3	0	12
Hoffmann sign	14	5	5	2	4
Babinski sign	19	5	1	2	13
Position sense	9	3	1	0	5
Vibration sense	11	8	2	1	1
Pin perception	1	1	0	1	0
Cotton perception	7	2	1	1	4
Nystagmus	15	6	1	0	8
Optic disks	12	0	2	1	10
Speech	7	0	0	0	7
Bladder status	19	3	2	1	14
Totals	265	66	39	19	160
Subjective status		8	5		10

Of the 66 instances in which signs of improvement appeared, 29 were accounted for by the same five criteria previously referred to, namely, gait, strength, cerebellar signs, clonus and vibratory sense. Among these same five criteria, there were 22 instances of regression. For example, there was improvement in gait in 4 cases (regression in 4); improvement

in strength in 3 cases (regression in 5); improvement in cerebellar signs in 8 cases (regression in 7); improvement in clonus in 6 cases (regression in 6), and improvement in vibratory sense in 8 cases (regression in 3). It is interesting, although unexplained, that the improvement in vibratory sense should be so consistent.

It is significant to compare the results of the three week period of therapy, in which there were 69 signs of improvement and 39 instances of regression, with the results of the long term study, in which there were 66 signs of improvement and 58 instances of regression. It would appear that the early preponderance of signs of improvement is more apparent than real and, as suggested, may be due in part to the three week period of bed rest. This is even more apparent when it is realized that most of the patients who were not followed for the longer periods were the severely disabled patients who were bedridden most of the time.

There seems to be a pronounced lability of certain signs in multiple sclerosis. Almost half the total changes occurred among five criteria. The changes were in both directions—some patients improving and others regressing. Even more striking was the frequent appearance of simultaneous signs of improvement and regression in the same patient. The inference from the foregoing data is that the changes observed reflected the natural course of the disease rather than the effect of specific therapy.

In addition to comparing the findings before and after arbitrary periods of treatment, we studied the interval events which occurred during therapy. The most striking feature thus observed was the appearance in several patients of distinct episodes of gross, new pathologic signs. These episodes occurred while the patients were under treatment, and their course was much the same as our experience would teach us to believe might be expected in this disease. For example, there occurred a transient episode of monoparesis, several episodes of spastic paraplegia and one of acute, gross cerebellar ataxia in a single extremity. Other patients showed progressive deterioration in spite of continued treatment. This, in our opinion, is additional evidence that tetraethylammonium chloride can prevent neither the occurrence of new manifestations nor the progression of those already present. A number of patients were seen with gross spasms of the lower extremities. These were not influenced by tetraethylammonium chloride.

SUBJECTIVE ANALYSIS

An effort was made to assess the degree of improvement from the patients' own statements. In the original group of 42 patients treated for a three week period in the hospital, 23 felt that they were improved; 18 felt no different, and 1 felt worse. In the long term follow-up observation on the 23 patients, only 8 felt better; 10 thought there was no

change, and 5 felt worse. Of the remaining 19 patients, only 8 continued to receive treatment. These were not followed by us, and their status was evaluated by letter. Of these 8 patients, 3 thought that they were better; 2 were worse, and the condition of 3 was unchanged.

It is thus seen that even in the subjective analysis there is a significant difference between the results of the short term and those of the long term observation. Of the 42 patients studied for the three week period, 23 felt improved and 1 felt worse, whereas of the 31 patients followed over a longer period only 11 felt better and 7 felt worse. Since the long term follow-up study revealed almost as many patients who felt worse as those who felt better, it is believed that the early subjective improvement may be related to the enthusiasm of the chronically ill patient for treatment rather than to any specific effect of that treatment.

SUMMARY AND CONCLUSIONS

A critical method of objective evaluation of therapy in multiple sclerosis is presented. It is believed that this approach may be of value in determining the effectiveness of treatment in other chronic neurologic diseases.

A group of 42 patients with multiple sclerosis was treated intensively with tetraethylammonium chloride in the hospital for three weeks. At the end of this period, among the original 466 pathologic findings, there were 69 signs of improvement, in 32 patients, and 39 signs of regression, in 20 patients. At this time 23 of these patients were subjectively improved and 1 felt worse. The condition of the others was unchanged.

A long term personal follow-up study of 23 of the original 42 patients for three to thirty months of treatment revealed that of 265 pathologic signs, 66 improved, in 21 patients, whereas 58 regressed, in 18 patients. In this group, 8 patients were subjectively improved, 5 felt worse and 10 noted no change. Of 8 other patients who continued to receive treatment and were followed only by letter, 3 reported that they were better, 2 were worse and the condition of 3 was unchanged. Thus, of 31 patients, a total of 11 felt better and 7 felt worse.

The reasons for the suggestive improvement, both objective and subjective, seen early in the course of treatment are discussed. The improvement was shown to be more apparent than real. Further follow-up observations on treatment revealed no significant difference between signs of improvement and regression, either objective or subjective.

The conclusion, therefore, is drawn that tetraethylammonium chloride has no influence on the course of multiple sclerosis.

Parke, Davis & Company supplied a generous amount of their brand of tetraethylammonium chloride (etamon® chloride), thus permitting the major part of this study to be carried out without cost to the patients.

FREQUENCY OF MULTIPLE SCLEROSIS IN GREATER NEW YORK

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IT HAS been noted during the past decade that an increasing number of cases of multiple sclerosis are coming to the attention of neurologists, ophthalmologists and general practitioners. Various attempts have been made in the past by different observers to obtain statistical data on this disease (von Hoesslin,[1] Brown and Putnam,[2] Sachs and Friedman [3]). Those observations, however, were never on a large enough scale to give a clear picture of the distribution of multiple sclerosis. It has, therefore, not been possible to determine whether or not an actual increase in the number of patients is taking place or whether improved medical care and examining methods have had their share in revealing cases of the disease which previously had remained undiagnosed.

The only statistical figures on a nationwide basis which so far are available come from Switzerland. There, Ackermann [4] found an incidence of 4 to 5 cases per 10,000 of the population, which, as we shall show, corresponds roughly to our own findings.

Our material was collected from most of the larger hospitals [5] in Greater New York by extracting the pertinent points from all available case histories covering the past ten years. Patients from smaller institutions and those who were under only private care were not included in this survey. On the other hand, the constant shift of population has brought people from different parts of the country to the hospitals of

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1. von Hoesslin, R.: Ueber multiple Sklerose: Exogene Aetiologie, Pathogenese und Verlauf, Munich, J. F. Lehmanns Verlag, 1934.

2. Brown, M. R., and Putnam, T. J.: Remissions in Multiple Sclerosis, Arch. Neurol. & Psychiat. **41**:913 (May) 1939.

3. Sachs, B., and Friedman, E.: General Symptomatology and Differential Diagnosis of Disseminated Sclerosis, J. Nerv. & Ment. Dis. **55**:391, 1922.

4. Ackermann, A.: Die multiple Sklerose in der Schweiz: Enquête von 1918-22, Schweiz, med. Wchnschr. **52**:1245, 1931.

5. Neurological Institute of the New York, Montefiore Hospital for Chronic Diseases, Bellevue Hospital and Kings County Hospital (Brooklyn).

this city and has thereby increased the number of our series. All charts with a doubtful diagnosis were omitted, but since we did not limit this investigation to cases verified by necropsy, we are well aware that a certain number are not cases of multiple sclerosis, though we accepted only those in which the patients had been seen by competent neurologists.

The total number of cases so collected was 4,898. The population of Greater New York is at present roughly 7,888,000, so that the incidence of this disease amounts to 6 in 10,000 hospitalized patients.

Of the series 2,805 were females and 2,093 males. The female patients, therefore, made up 57.47 per cent of the total. The numerical ratio of New York's population being 50.8: 49.2 per cent in favor of the female sex, our figures indicate that multiple sclerosis is evenly distributed between the sexes. Carter, Sciarra and Merritt,[6] who limited their survey to cases with autopsy, obtained similar results.

It has previously been reported by Miura,[7] Sprawson [8] and Verhaart [9] that multiple sclerosis is extremely rare among the Japanese and in the Netherland East Indies. Snapper [10] stated that he had never seen a case of the disease during his stay in China. Lyman [11] reported that he saw cases of neuromyelitis optica among his Chinese medical students at the University of Peiping. Yu-Lin Ch'eng [12] pointed out that multiple sclerosis is rare among the Chinese and generally takes the acute form, involving relatively young persons. Steiner,[13] Bailey [14] and Brickner and Brill [15] came to the conclusion that multiple sclerosis was relatively rare among American Negroes, while Kolb,[16] in a survey of Baltimore, could not confirm these findings. He found that the incidence among

6. Carter, S.; Sciarra, D., and Merritt, H. H.: The Course of Multiple Sclerosis as Determined by Autopsy Proven Cases, A. Research Nerv. & Ment. Dis., Proc. (1948) **28**:471, 1950.

7. Miura, K.: In discussion on Nonne, M.: Serologisches zur multiplen Sklerose, Deutsche Ztschr. f. Nervenh. **41**:146, 1911.

8. Sprawson, C.: Disseminated Sclerosis Amongst Indians in India, Far East A. Trop. Med., Tr. Seventh Cong. 1927 **1**:8, 1928.

9. Verhaart, W. J. C.: Ophthalmo-Neuromyelitis, multiple und diffuse Sklerose bei Ost-Asiaten in Niederl. Ost-Indien, Acta psychiat. et neurol. **13**:93, 1928.

10. Snapper, I.: Oral communication to the authors.

11. Lyman, R. S., citing Wei-Yu-Lin (article in Chinese, reporting on 40 to 50 patients seen in Peiping in four to five years).

12. Yu-Lin Ch'eng, L.: Private communication to the authors. Dr. Yu-Lin Ch'eng is director of the National Neuropsychiatric Institute, Ministry of Health, Nanking, and professor of neurology and psychiatry at the University of Nanking.

13. Steiner, G.: Multiple Sclerosis: The Etiological Significance of the Regional and Occupational Incidence, J. Nerv. & Ment. Dis. **88**:42, 1938.

14. Bailey, P.: Incidence of Multiple Sclerosis in United States Troops, Arch. Neurol. & Psychiat. **7**:582 (May) 1922.

15. Brickner, R. M., and Brill, N. Q.: Dietetic and Related Studies in Multiple Sclerosis, Tr. Am. Neurol. A. **66**:157, 1940.

16. Kolb, L.: Multiple Sclerosis in the American Negro, Arch. Neurol. & Psychiat. **47**:413 (March) 1942.

the native Negro population corresponded exactly with that of the American white group. From a limited survey of the Negro population (our investigation did not cover the hospitals in the Negro districts), it would appear that they show much less multiple sclerosis than white racial groups of various ancestries.

It was interesting to note the relatively high incidence among Asiatics in New York, as compared with that reported from Asia. The small total of the observed cases, however, precludes a statistical evaluation. With respect to the white population of various national origins, the incidence of multiple sclerosis in any particular group appears to coincide with the percentage of the total population represented by persons of the respective extractions living in New York city (chart 1).

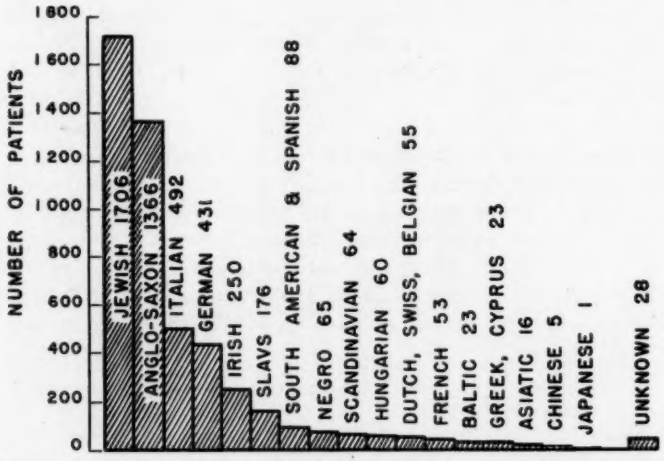

Chart 1.—Racial distribution of patients with multiple sclerosis in Greater New York.

It has always been claimed that in the vast majority of cases the disease starts at an early period of adult life. We found the onset of multiple sclerosis most frequent between the ages of 26 and 30, but almost the same figures were encountered for the age group of 21 to 25 and only a slightly lower figure for the group between the ages of 31 and 35. A still relatively large number of patients had onset of this disease between the ages of 36 and 40 and 16 and 20 (chart 2). These figures coincide with the findings in cases verified at autopsy by Carter, Sciarra and Merritt.[6] Eight patients had their first symptoms before the age of 10 years. In all of them the course of the disease indicated, and in 2 of them the postmortem findings confirmed, the diagnosis. In the age group of 51 to 55, a diagnosis of multiple sclerosis was made for 27 patients and later confirmed by the subsequent course or by autopsy.

All these figures support the view that multiple sclerosis is mainly a disease of the young adult. It may, however, start at any other time of life.

Psychogenic factors, such as worry and "nervous breakdown," were claimed by 236 patients as responsible for the onset of their disease. This figure is relatively small, and the causal relation in many instances appears to be very loose. We think this observation to be rather important, since Grinker, Ham and Robbins [17] stressed the part that psychologic influences and behavior patterns play in multiple sclerosis.

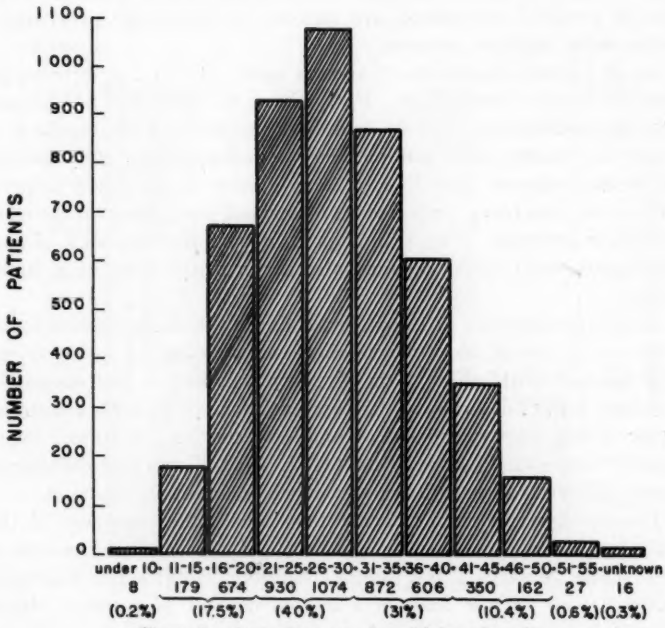

Chart 2.—Age of onset of multiple sclerosis.

Sixty-four patients claimed that climatic changes, especially a shift to a colder climate, had brought on the disease. Limburg [18] pointed out that climate played an important part in several cases, and an isotherm of 66 F. was put down as a kind of borderline for the occurrence of the disease. It was thought that multiple sclerosis was often encountered north of it whereas the disease was said to be rare south of that line.

17. Grinker, R. R.; Ham, G., and Robbins, F.: Some Psychodynamic Aspects of Multiple Sclerosis, A. Research Nerv. & Ment. Dis., Proc. (1948) **28**:456, 1950.

18. Limburg, C.: The Geographic Distribution of Multiple Sclerosis and Its Estimated Prevalence in the United States, A. Research Nerv. & Ment. Dis., Proc. (1948) **28**:15, 1950.

Pregnancy was held responsible for the onset of multiple sclerosis by 31 women, and abortion, by 19 women. Four hundred and twelve women with multiple sclerosis, however, had had one or more children in the years prior to the onset of their symptoms. Two hundred and forty-two of these had several children. Among women who already had multiple sclerosis, 316 became worse after childbirth and 35 after abortion. The question whether multiple sclerosis is an indication for termination of pregnancy and whether patients with the disease should have children cannot be decided on the strength of these figures. In spite of the statistical material collected by Tillman,[19] we, on the basis of personal experience, are inclined to discourage pregnancy in women with multiple sclerosis.

In 20 patients operations of various kinds, and in 113 injuries, preceded the onset of the disease. Forty-six of the latter had head injuries with unconsciousness, and 61 had back injuries. One hundred and twenty-two patients with multiple sclerosis became worse after operation and 64 had relapses after injury. This number is too small to permit conclusions concerning the influence of surgical procedures on the course of multiple sclerosis. These findings do not support the view of many neurologists, who advise against the performance even of a lumbar puncture.

It is interesting that in 10 patients children's diseases, such as mumps (3 patients), scarlet fever (4 patients) and measles (3 patients), preceded the immediate onset of the disease. It is known that encephalitis after such infections leads to perivascular myeloclasis with a histologic picture closely resembling that of multiple sclerosis. A survey by van Bogaert,[20] confirmed by one of us, (H. H.) has shown that the sequelae of these children's diseases hardly ever precede multiple sclerosis.

Twenty-eight patients reported that some other member of their family had multiple sclerosis. We did not, however, have records on any of these relatives. We cannot, therefore, confirm the findings of Mackay,[21] who, on the basis of a limited number of patients, claimed rather high figures for a familial incidence.

Three hundred and thirty-six patients, or 6.6 per cent, showed various manifestations of allergy, and 127 had relatives with allergic diseases. A large part of the latter group were allergic themselves. The hypothesis was brought forward by Glanzman,[22] Lher-

19. Tillman, A. J. B.: The Effect of Pregnancy on Multiple Sclerosis and Its Management, A. Research Nerv. & Ment. Dis., Proc. (1948) **28**:548, 1950.

20. van Bogaert, L.: Les manifestations nerveuses au cours des maladies éruptives (varicelle, rougeole, scarlatine), Rev. neurol. **59**:150, 1933; Histopathologische Studie über die Encephalitis nach Windpocken (Encephalitis postvaricellosa), Zentralbl. f. d. ges. Neurol. & Psychiat. **140**:201, 1932.

21. Mackay, R. P.: The Familial Occurrence of Multiple Sclerosis and Its Implications, A. Research Nerv. & Ment. Dis., Proc. (1948) **28**:150, 1950.

22. Glanzman, E., cited by Hurst, E. W.: Brain **67**:103, 1944.

mitte and Fribourg-Blanc,[23] Kennedy,[24] Pardee,[24a] Hurst,[25] Baer and Sulzberger [26] and others that some form of allergy may act as an important pathogenetic factor in multiple sclerosis. The figures of this survey show that the frequency of allergic manifestations in patients with multiple sclerosis corresponds with the average incidence of allergy in the total populations.

Four hundred and forty-three patients showed rapid progression, and 2,048 slow progression, of their signs and symptoms. Remissions occurred in 2,062 cases, and in 345 the disease was stationary (chart 3 *A*). Without consideration of how long individual patients had had

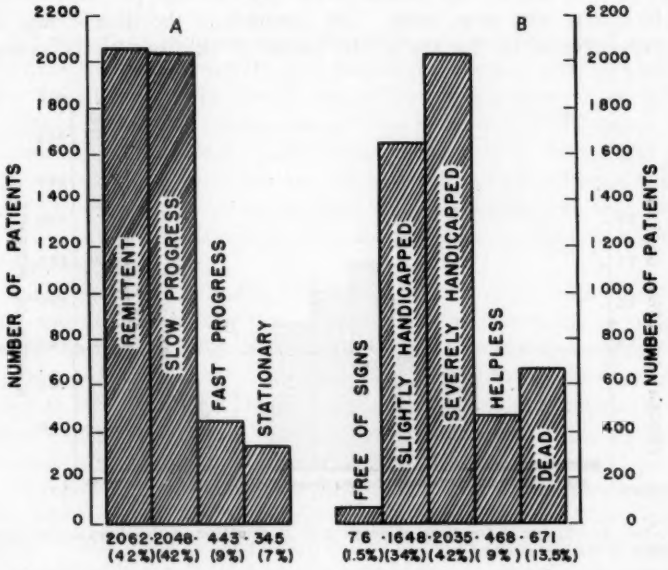

Chart 3.—*A*, course of the disease and, *B*, condition of the patient in a series of cases of multiple sclerosis.

the disease, the last examination revealed 76 to be free of signs, 1,648 slightly handicapped, 2,035 severely handicapped, 468 bedridden and

23. Lhermitte, J., and Fribourg-Blanc: Encéphalomyelite subaiguë consécutive à la vaccination antiamarile, Rev. neurol. **65**:391, 1936.

24. Kennedy, F.: Allergic Manifestations in the Nervous System, New York State J. Med. **36**:469, 1936.

24a. Pardee, I.: Allergic Reactions in the Central Nervous System, Arch. Neurol. & Psychiat. **39**:1360 (June) 1938; J. Nerv. & Ment. Dis. **88**:91, 1938.

25. Hurst, E. W.: A Review of Some Recent Observations on Demyelination, Brain **67**:103, 1944.

26. Baer, R. L., and Sulzberger, M. B.: Role of Allergy in Multiple Sclerosis, Arch. Neurol. & Psychiat. **42**:837 (Nov.) 1939.

helpless and 671 dead (chart 3 *B*). Of these 671, most patients, i. e., 64 per cent, died after an illness of ten to twenty-five years and 184 (27 per cent) after a duration of six to ten years. The age at the time of death did not show any variation from that of death from all causes (chart 4).

According to Carter, Sciarra and Merritt,[8] the average duration of life was thirteen years. The shortest duration was eight weeks; the longest, sixty-four years. Forty per cent of their patients died within the first ten years, and a total of 66 per cent, within the first fifteen years. These figures correspond with ours. Seventy-two per cent of their patients had become incapacitated. The average period from onset to incapacity was nine years. The duration of the disease was only slightly affected by the age of the patient at the time of the onset of

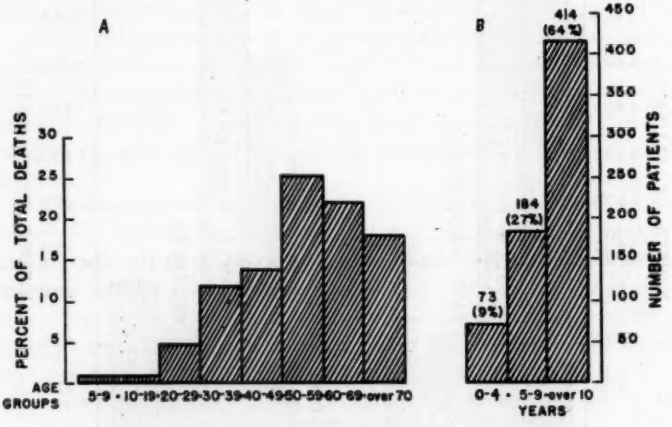

Chart 4.—*A*, age at the time of death and, *B*, duration of the disease until death in cases of multiple sclerosis.

symptoms. The later the age of onset of the disease, the less was the loss of normal expected years of life.

With respect to frequency of signs in multiple sclerosis, this survey shows that cerebellar signs occupy the first place, with signs of involvement of the optic nerve second and of sensory changes third. Again comparing our observations with those of Carter and co-workers, we find that they noted ocular manifestations in 100 per cent of their material, alterations in deep reflexes in 98 per cent, loss of superficial reflexes in 96 per cent, ataxia in 93 per cent, abnormal reflexes in 91 per cent, changes in muscular tone in 85 per cent, impairment of vibration sense in 85 per cent and loss of position sense in 78 per cent.

The tendency to remission was most frequently found with impairment of visual acuity and diplopia, next with objective and subjective sensory changes and least with cerebellar signs. Again we found, in

accordance with the observations of Carter and his co-workers, that the initial manifestations were more likely to remit than those which occurred late in the course of the disease. A single initial symptom was more likely to disappear than was an initial complex of symptoms.

CONCLUSIONS

In a statistical survey of cases of multiple sclerosis in Greater New York, an attempt has been made to evaluate the incidence of this disease. It was thought that such an undertaking should be especially interesting in view of the fact that there is hardly a place anywhere in the world in which so many people of the most different racial extractions can be found.

Living factors and nutritional conditions, on the other hand, may be said to be more uniform here than elsewhere. A total of 4,898 patients were investigated. The distribution of the disease between the sexes was about equal. No predilection for any racial or national group was encountered. Only Negroes showed a deviation from the general distribution. In New York city the incidence of multiple sclerosis among the white population, including those of every extraction, was found to be about 6 in 10,000, whereas that for the Negro population was only 1.4 in 10,000.[27]

Since it had been stated that the disease is rarely encountered in Italy and the South American countries, it was interesting to observe that the Italians of New York, who hail mostly from the southern parts of Italy, and the South American population showed the same incidence as other groups. The age distribution of multiple sclerosis coincided with the findings of other authors, who observed that the onset was most frequent in younger adults.

A relatively high number of patients with continuous slow progression was found, while those with remissions still showed the largest figure. Early onset of the disease carried a better prognosis with regard to remission than onset in later life, which was associated with a greater tendency to a slowly progressive or stationary course.

Allergic conditions were not found to be more frequent among patients with multiple sclerosis than among those with other diseases. The influence of pregnancy, abortion, operations or injuries on the onset of the disease could not be confirmed. We believe, however, that they may play an important part in producing relapses.

Relations between the disease and psychologic or emotional factors could not be evaluated.

The age at the time of death of patients with multiple sclerosis did not deviate much from the average mortality figures for the various decades, and most deaths occurred from intercurrent diseases, and not from multiple sclerosis.

710 West One Hundred and Sixty-Eighth Street (Dr. Chiavacci).

27. The death rate among the Negroes, however, was remarkably high.

HISTOLOGIC OBSERVATIONS ON THE SUPRADIAPHRAGMATIC PORTIONS OF THE VAGUS NERVES

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VAGECTOMY for the treatment of peptic ulcer is in the stage of clinical trial, and final conclusions as to its place in therapy are not yet warranted. The gross anatomy of the supradiaphragmatic portion of the vagus nerves and the psysiologic changes that follow their resection have been carefully studied and reported. However, the literature contains only one reference to microscopic study of the portions of nerve removed at operation, and in this report [1] no deviations from the normal were described. The purpose of this communication is to present the microscopic observations in specimens of vagus nerves removed at operation from patients with duodenal ulcer. These findings are compared with those encountered in a series of specimens of the same portion of the nerves removed at autopsy from persons showing no evidence of any pathologic condition in the gastrointestinal tract.

In evaluating the results of this study, it is to be noted that only a relatively small part of the peripheral portions of the vagus nerves are made available for microscopic study by the usual surgical vagectomy. Histologic abnormalities found in the 5 cm. of nerve lying immediately above the diaphragm might not be associated with any significant changes in the remaining nerve or its nuclei. On the other hand, and even more disturbing, is the possibility that significant pathologic change in the nuclei or the upper part of the nerve might be present when the supradiaphragmatic portion shows no deviation from the normal.

Further difficulty in the interpretation of the results of a study of this kind is the problem of establishing the significance of deviations from the usual microscopic picture. In the numerous studies that have

This study was aided by a grant from the Lydia Raymond Research and Publication Fund of the Framingham Union Hospital.

From the Departments of Pathology and Surgery, Boston University School of Medicine, and the Pathological and Surgical Services of the Framingham Union Hospital.

1. Epstein, J. A.: J. Mt. Sinai Hosp. **15**:83, 1948.

been made on the sympathetic ganglia [2] the same problem has been encountered. Bergmann and associates [2f] stated:

> Critical evaluation of the literature leads to the sobering conclusion that almost every finding in ganglia from patients suffering from a certain disorder can be observed in ganglia of persons not afflicted with the disease in question.

A similar situation probably exists in the vagus tract, and changes that are now considered to be of pathologic significance may be shown to be variations of the normal.

With these reservations, the results of this study suggest that an organic pathologic process may be demonstrable in the supradiaphragmatic portions of the vagus nerves more frequently when duodenal ulcer is present than when it is not present. This, in turn, suggests that the "cephalic" phase of gastric hypersecretion commonly encountered in patients with duodenal ulcer may at times be due to irritating lesions in the peripheral portions of the vagus nerves. Although the material available for this study is relatively small, it is presented with the hope that those who have a greater number of cases at their command may provide evidence from which more concrete conclusions can be drawn.

MATERIAL AND METHODS

The supradiaphragmatic portions of the vagus nerves removed at operation in 21 patients with duodenal ulcer were subjected to histologic study. In each of these patients vagectomy was performed because of a long-standing history of duodenal ulcer, which was intractable to medical management. In an additional patient who died of peritonitis following perforation of a duodenal ulcer, the nerves were removed at autopsy. In 5 of the 22 cases of duodenal ulcer only a single nerve tract was available, the remaining nerve having been lost or utilized for making routine or frozen sections. In the remaining 17 cases the excised portions of both nerves were studied. Sixteen of the patients were men and 6 were women, and their ages varied from 31 to 71 years.

A control series of vagus nerves removed from patients without duodenal ulcer were also studied. This material was obtained at autopsy and, like the surgical material, consisted of the terminal 5 cm. of the supradiaphragmatic portions of the vagus nerves. One nerve removed during the transthoracic repair of a diaphragmatic hernia in a patient with no clinical or roentgenologic evidence of ulcer was added to the control series. No evidence of duodenal or gastric ulcer was found in any of the cases in which autopsy was performed, although gross and/or microscopic evidence of atrophic gastritis was present in 4. The ages at the time of death ranged from a stillbirth to 90 years.

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2. (*a*) DeCastro, F.: Sympathetic Ganglia, Normal and Pathological, in Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 1, pp. 319-329. (*b*) Kuntz, A.: Sympathetic Ganglions Removed Surgically: A Histopathologic Study, Arch. Surg. **28**:920 (May) 1934; (*c*) Am. J. Path. **14**:783, 1938. (*d*) Truex, R. C.: ibid. **16**:255, 1940. (*e*) Bergmann, L.: Anat. Rec. **85**:117, 1943. (*f*) Bergmann, L. L.: Harman, P. J.; Pick, J., and Wertheim, H. M.: Surgery **24**:695, 1948.

All nerves were embedded in paraffin, sectioned both horizontally and transversely at different levels and stained with hematoxylin and eosin. When sufficient material was available, the study was completed on frozen sections stained by the Cajal reduced silver method for the nerve fibers and by the Spielmeyer method for the myelin sheaths.

THE VAGUS NERVES

Gross anatomic studies of the periesophageal plexus formed by the vagus nerves at the esophagogastric junction have been reported by McCrea,[3] Hovelacque,[4] Bradley and associates,[5] Miller and Davis[6] and Doubilet, Shafiroff and Mulholland.[7] The last authors concluded that, in general, the periesophageal vagus plexuses conform to four well defined types: "those in which the right and left vagi communicated through anterior fibers; those in which no communicating fibers could be found; those in which communicating fibers were all posterior, and those in which communicating fibers were present both posteriorly and anteriorly."

According to Schafer,[8] the vagus nerve, at its exit from the skull, contains large, medium and small fibers. The large fibers innervate chiefly the pharynx and larynx, and very few reach the distal portion of the esophagus and the stomach. The latter are chiefly supplied by nonmedullated fibers and by small and medium-sized medullated fibers. These findings are in general agreement with those of McSwiney and Spurrell,[9] who studied the distribution of the myelinated fibers of the vagus nerves of the cat. They found that the proportion of myelinated fibers diminishes progressively as the nerves proceed distally and that the abdominal branches consist almost entirely of nonmedullated fibers. Similar conclusions have been reached by Gaskell[10] and by Foley and DuBois.[11] While accurate fiber counts were not attempted in the specimens used in this study, it was noted that only a limited number of myelinated fibers were present at the usual site of supradiaphragmatic resection.

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4. Hovelacque, A.: Anatomie des nerfs craniens et rachidiens et du systeme grand sympathique ches l'homme, Paris, Gaston Doin & Cie, 1927.
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7. Doubilet, H.; Shafiroff, B. G. P., and Mulholland, J. H.: Ann. Surg. **127**:128, 1948.
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OBSERVATIONS

Damage to peripheral nerves without loss of anatomic continuity frequently results in spindle-shaped neuroma, perineural thickening, dense intramural fibrosis or epineural hemorrhage.[12] The changes encountered in our cases were predominantly of this kind.

Figure 1, a cross section of the right vagus nerve removed by the transthoracic route from a woman aged 52, whose history of ulcer

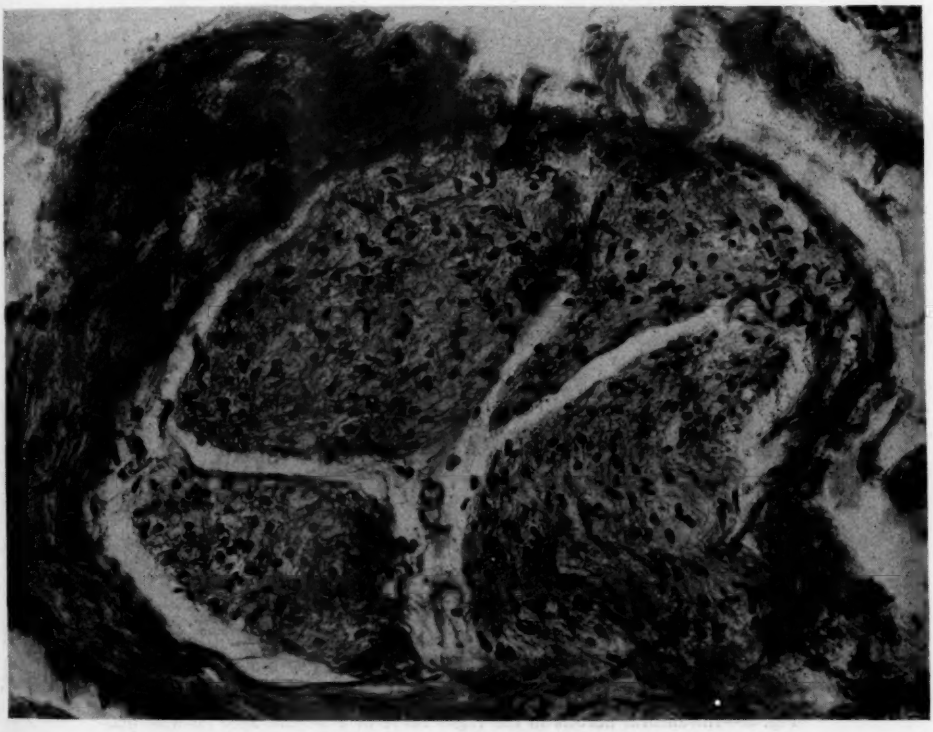

Fig. 1.—Perineural fibrosis in the vagus nerve from a woman aged 52 with duodenal ulcer.

dated back eight years, is a clearcut illustration of perineural fibrosis. The fibrous thickening was irregular in distribution and formed plaques at the periphery of the nerve bundle. Some of these plaques were poor in cells, while others showed prominent proliferation of mesenchymal cells, chiefly of fibroblasts. In some places the fasciculi were intact,

12. Seddon, H. J.: Brain **66**:237, 1943.

while in some others the endoneurium took on a dense stain for collagen and was abnormally cellular, owing to the proliferation of oval, pale-stained neural fibroblasts.

Figure 2, a cross section from the vagus nerve removed from a man aged 60 with a long history of duodenal ulcer, shows thick bands of rather acellular and poorly vascularized fibrous connective tissue

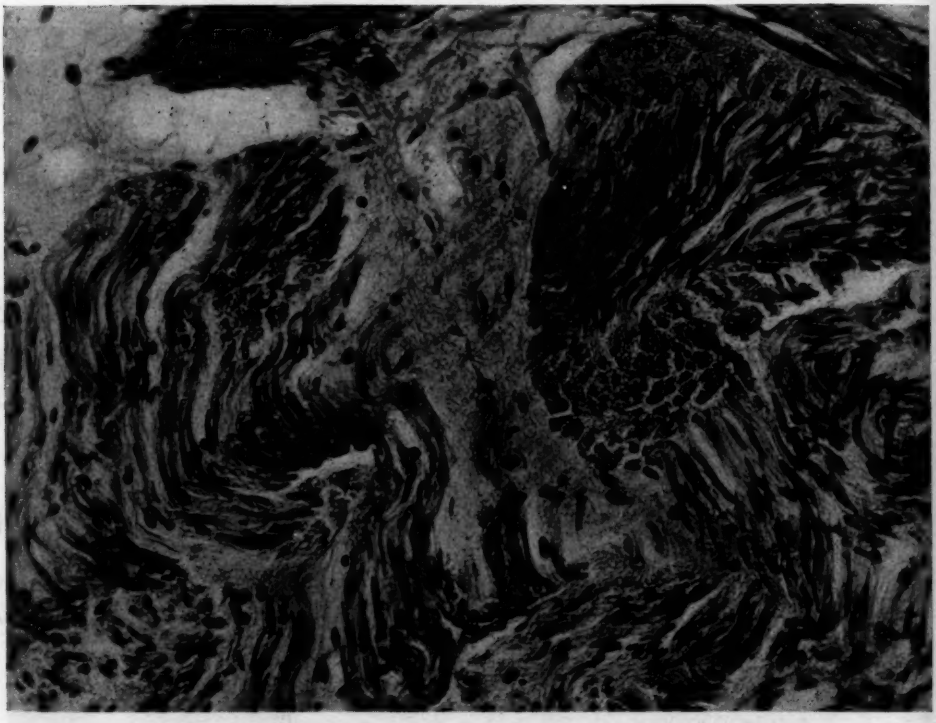

Fig. 2.—Intraneural fibrosis in the vagus nerve of a woman aged 60 with duodenal ulcer. Note scar extending deep into the nerve.

extending from the perineural membrane into the nerve bundle and giving rise to deep scarring. Within the scarred area the nerve fibers were almost completely obliterated, and where they were still recognizable they appeared fragmented and widely separated. Sections stained by the Cajal method showed terminal swellings and clublike formations (bulbs of retraction) of the fragmented fibers in the immediate vicinity of the areas of scarring. In other parts of the same

specimen the nerve bundles were edematous, with widely distended perineural spaces and patchy areas of increased cellularity, caused by the proliferation of neural fibroblasts (fig. 3).

Figure 4 illustrates even more pronounced scarring, in a nerve removed from a man aged 46 with a long history of duodenal ulcer. The collagen proliferation and sclerosis were here accompanied with

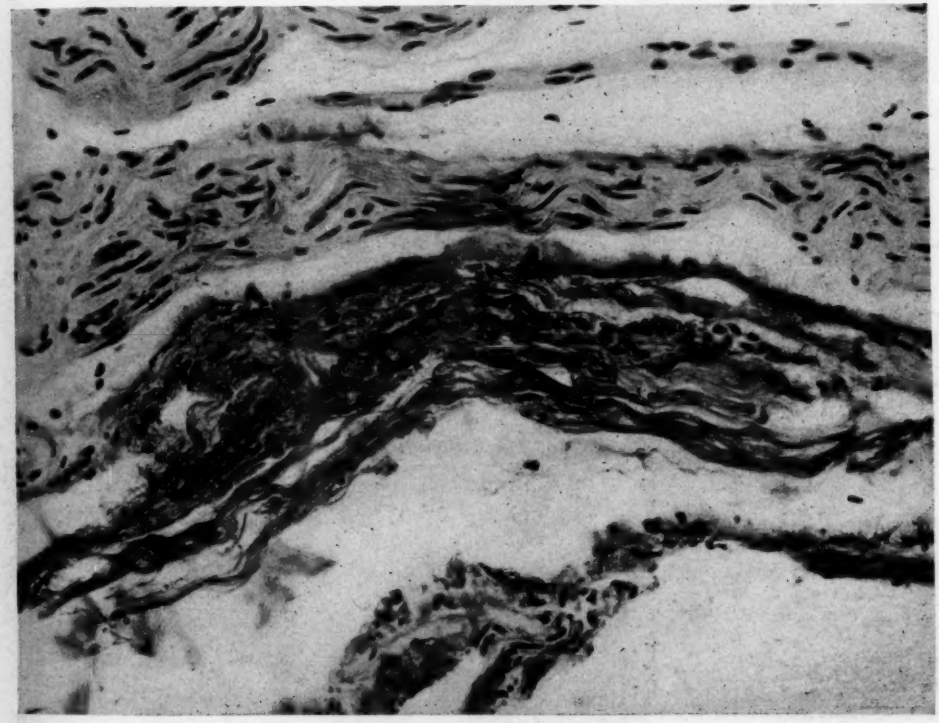

Fig. 3.—Longitudinal section of the same nerve as that shown in figure 2. Note edema of nerve bundles and areas of increased cellularity.

severe damage to the nerve fibers, which at many points were reduced to mere granular tracts outlining the course of the disintegrated structures. These changes were not diffuse, as fascicles or groups of fascicles with evidence of damage alternated with similar structures which appeared normal.

Figure 5 illustrates another microscopic pattern which may be abnormal. The specimen was removed from a man aged 52 with a

history of duodenal ulcer of ten years. The perineural spaces were greatly distended and were occupied to a considerable extent by areolar adipose tissue. The nerve bundles were pushed aside and frequently

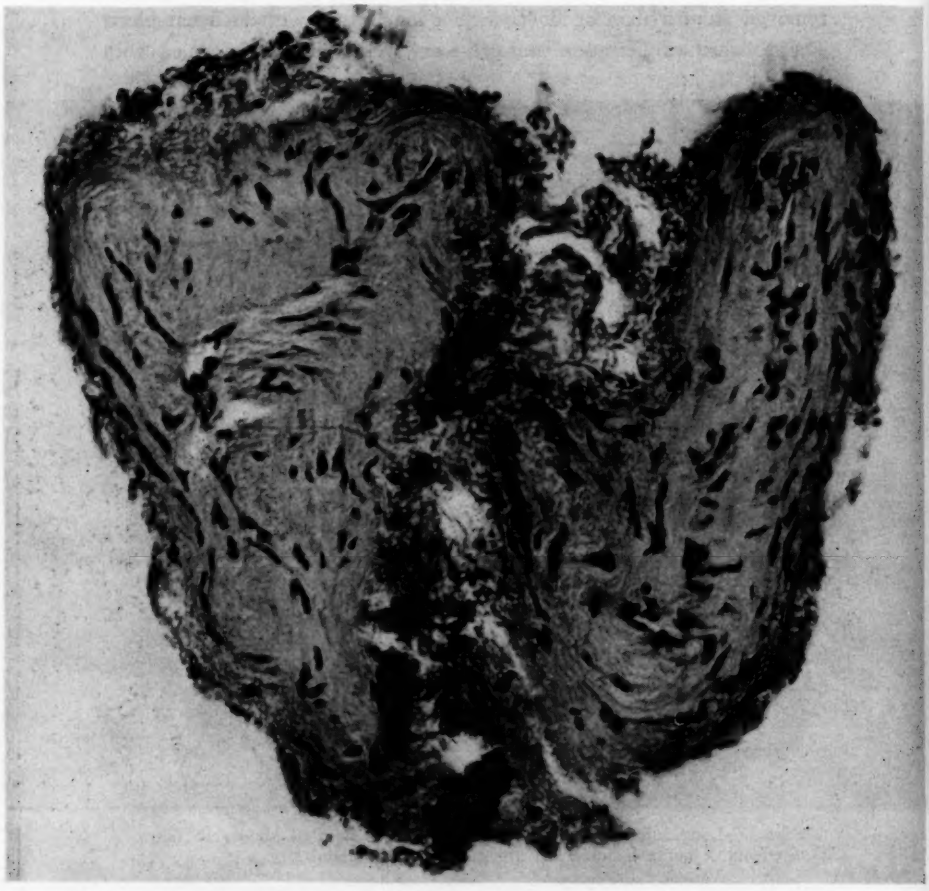

Fig. 4.—Cross section of vagus nerve from a man aged 46 with duodenal ulcer. Note deep scarring and damage to nerve fibers.

showed widely spaced fascicles. There was no evidence of fibrosis, scarring or proliferation of fibroblastic cells, and the axis-cylinders were apparently intact. However, gaps in the myelin sheaths and beading of myelin were noted in scattered areas. These lesions were

suggestive of neuron atrophy, and possibly the intraspatial proliferation of areolar tissue was compensatory.

A more definite pathologic change is illustrated in figure 6. This shows a longitudinal section from a vagus nerve removed by the transthoracic route from a woman aged 38 whose symptoms of duodenal ulcer were severe and extended over a period of four years. Beading

Fig. 5.—Cross section of nerve from a man aged 52 with duodenal ulcer. Note wide perineural space, containing edematous areolar tissue.

of myelin and large gaps in the myelin sheaths are readily identified, while the preparations stained by the Spielmeyer method revealed moniliform swelling and fragmentation, with areas of reabsorption or resolution into round, oval or irregularly shaped globules. The axons were thickened, followed a spiral course and showed occasional corkscrew twisting with formation of peculiar loops. Alternating pale and deeply stained segments were frequently noted in the same fibers, and

the situation of the axons was indicated only by rows of granules. The focal distribution of these changes made it possible to observe, in the same microscopic field, axons in all stages of a progressive neurolytic process, as well as apparently intact axons. A few fat-filled phagocytes were noted, and the neural fibroblasts showed foci of active proliferation.

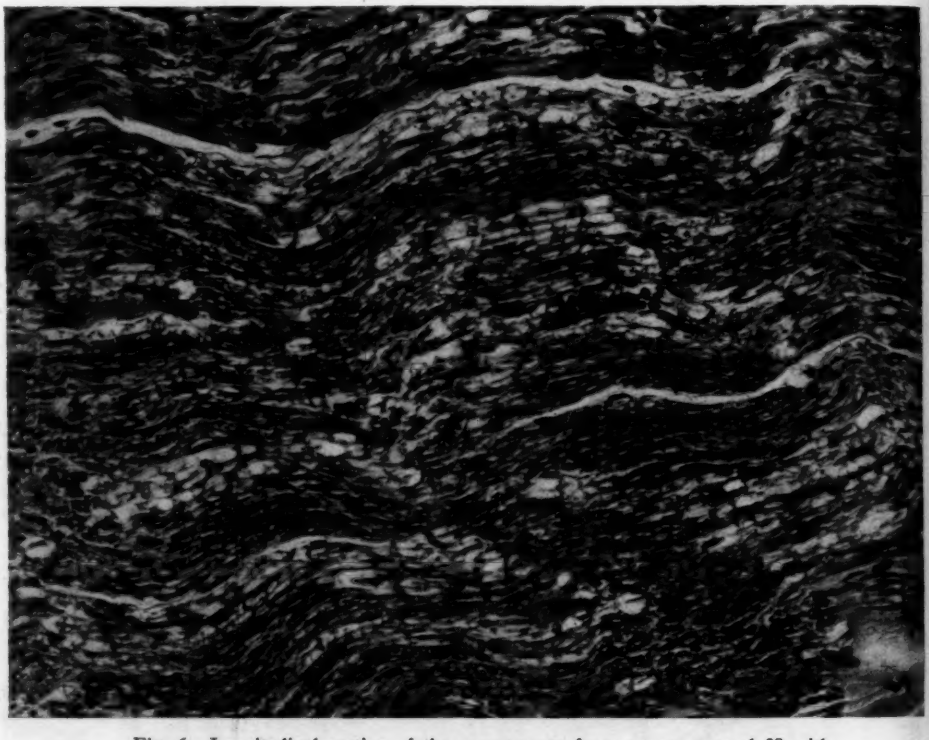

Fig. 6.—Longitudinal section of the vagus nerve from a woman aged 38 with duodenal ulcer. Note beading of myelin.

Figure 7 illustrates an acute inflammatory reaction in the vagus nerve removed by the transthoracic route from a man aged 47 whose history of duodenal ulcer extended over a period of five years. The inflammatory cells were chiefly granulocytes and in some areas were so numerous that they overshadowed the large segments of the fascicles. Even in areas in which the inflammatory cell infiltration was most extensive the axons were fairly well preserved. The few myelin sheaths, however, had a moniliform appearance, narrow segments alternating

with fusiform or ovoid swellings of various sizes. There was no visible proliferation of neural fibroblasts or of collagen fibers.

These illustrations indicate the types of pathologic changes encountered in this study. Of the 22 cases of duodenal ulcer, changes in the removed portions of vagus nerves were found in 14. Changes of a corresponding type were seen in 10 of the 30 control cases. In none of the

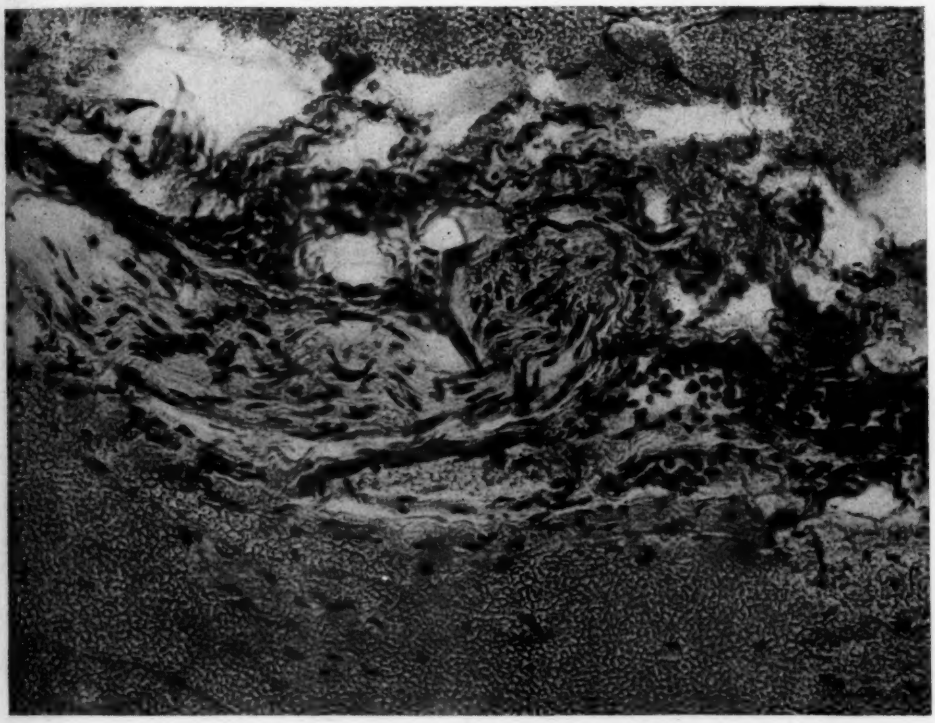

Fig. 7.—Inflammatory reaction in the vagus nerve from a man aged 47 with duodenal ulcer.

control cases was there evidence of gastric or duodenal ulcer, although gross and/or microscopic evidence of atrophic gastritis was present in 4. Of the cases of gastritis, only 1 showed pathologic change in the vagus nerve, and that consisted of intraneural fibrosis with deep scarring and is illustrated in figure 8. Tables 1 and 2 show the types of pathologic change in the vagus nerves found in the cases of ulcer and in the control series, respectively.

COMMENT AND CONCLUSIONS

Systematic histologic study of supradiaphragmatic portions of the vagus nerves removed at operation and autopsy has shown, in a number of instances, a gamut of lesions which include inflammatory cell infiltration, either intraneural or perineural, myelin degeneration, neurolysis, neuronal atrophy and perineural and intraneural fibrosis

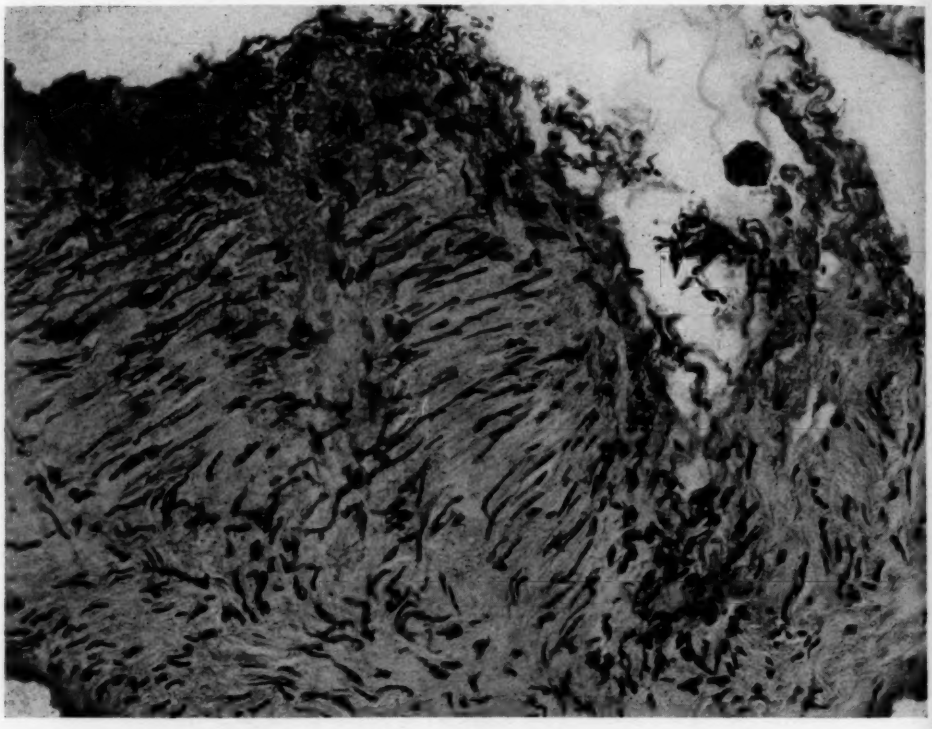

Fig. 8.—Fibrosis and scarring in a vagus nerve removed at autopsy from a man with atrophic gastritis.

and scarring. These changes have been found to be focal in distribution, resulting in an irregular alternation, often in the same microscopic field, of apparently normal fascicles and of fascicles displaying one, or a combination, of the aforementioned changes. Hemorrhage into or around the nerve, presumably incident to the trauma of its removal, was found in 6 of the surgical cases and in 2 of the autopsy cases.

Denny-Brown and his associates [13] have shown the susceptibility of the peripheral nerves to minimum trauma, including pressure and stretching. With the exception of the acute inflammatory reactions, such as that illustrated in figure 7, the pathologic patterns noted in this study indicate chronic, protracted processes. The nature of these changes would appear to exclude trauma, operative or otherwise, as an etiologic agent in their production. It is probable that the changes encountered

TABLE 1.—*Pathologic Changes Found in Vagus Nerves Removed from Patients with Duodenal Ulcer*

Case No.	Age	Sex	Inflammation		Myelin Degeneration	Neurolysis	Neuronal Atrophy	Fibrosis and Scarring	
			Intraneural	Perineural				Intraneural	Perineural
1	31	F	..	..	..	..	..	..	+
2	32	F	..	..	..	..	+	..	..
3	36	M	..	+	..	..	..	..	..
4	38	M	..	..	..	..	..	..	..
5	38	F	..	..	+	+	..	..	..
6	42	M	..	..	..	..	..	..	..
7	43	M	..	..	+	..	..	..	+
8	45	M	..	..	..	..	..	..	+
9	46	F	..	..	..	+	..	+	..
10	47	M	+	..	..	..	..	..	..
11	52	F	..	..	..	..	..	..	+
12	52	M	..	..	..	..	+	..	..
13	54	M	..	..	..	..	..	..	..
14	54	M	..	..	..	..	..	..	..
15	59	M	..	..	..	..	..	..	..
16	60	M	..	..	..	..	+	..	..
17	60	M	..	..	..	..	..	+	..
18	64	M	..	..	..	..	..	..	..
19	65	M	..	..	..	..	..	..	..
20	68	M	..	..	..	..	..	..	+
21	69	M	..	..	..	..	..	..	..
22	71	F	+	+	..	..	+	..	..

were caused by the same ill defined agents as those usually advocated in the explanation of comparable lesions in other peripheral nerves.

The presence of pathologic changes in some of the nerves removed from persons without ulcer, together with the fact that some patients with ulcer have apparently normal nerves, makes it evident that none of the changes encountered can be considered a *sine qua non* of the ulcer diathesis. It is to be noted, however, that in this small series

13. Denny-Brown, D., and Brenner, C.: J. Neurol., Neurosurg. & Psychiat. **7**:76, 1944. Denny-Brown, D., and Doherty, M. M.: Effects of Transient Stretching of Peripheral Nerve, Arch. Neurol. & Psychiat. **54**:116 (Aug.) 1945. Denny-Brown, D., and Brenner, C.: Paralysis of Nerve Induced by Direct Pressure and by Tourniquet, ibid. **51**:1 (Jan.) 1944.

TABLE 2.—*Pathologic Changes Found in Vagus Nerves from Patients Without Duodenal Ulcer*

No.	Age	Sex	Cause of Death	Inflammation		Myelin Degeneration	Neurolysis	Neuronal Atrophy	Fibrosis and Scarring	
				Intraneural	Perineural				Intraneural	Perineural
1	0	F	Stillborn; erythroblastosis fetalis	..	+	..	..	..	..	..
2	1	F	Pneumonia	..	..	..	..	..	..	..
3	5	F	Meningitis	..	..	..	..	..	..	..
4	13	M	Postoperative shock; intussusception	..	..	..	..	..	..	+
5	37	F	Chronic pyelonephritis; bronchopneumonia	..	..	..	..	..	..	..
6	42	M	Stem cell leukemia	..	..	..	..	..	..	..
7	42	M	Acute myocardial infarction	..	..	..	..	+	..	..
8	42	M	Malignant nephrosclerosis; acute pulmonary edema	+	..	.	..	..	..	..
9	47	F	Atrophic cirrhosis of liver	..	..	..	..	..	..	..
10	48	F	Patient living; nerve removed during repair of diaphragmatic hernia	..	..	..	..	..	+	..
11	48	M	Pneumonia	..	..	..	..	..	..	..
12	49	F	Atrophic cirrhosis of liver	..	..	..	..	..	+	+
13	54	M	Bronchogenic carcinoma with metastases to hilar nodes; atrophic gastritis	..	..	..	..	..	..	..
14	55	M	Lower nephron nephrosis	..	..	..	..	..	..	+
15	59	M	Acute myocardial infarction; atrophic gastritis	..	..	..	..	..	..	..
16	59	F	Carcinoma of stomach with metastases	..	..	..	..	..	..	..
17	60	M	Renal carcinoma with metastases	..	..	..	..	..	..	..
18	60	F	Cerebral hemorrhage	..	..	..	..	..	..	..
19	63	M	Arteriosclerotic heart disease; nephrosclerosis	..	..	..	..	..	..	..
20	64	M	Aortic aneurysm; bronchopneumonia	..	..	..	..	..	..	..
21	65	M	Lobar pneumonia	..	..	..	..	..	..	..
22	68	F	Atrophic cirrhosis of liver; large hiatus hernia present	..	..	+	..	..	..	..
23	72	M	Atrophic cirrhosis of liver	..	..	..	..	..	..	..
24	72	F	Arteriosclerotic heart disease	..	..	..	..	..	..	..
25	74	F	Carcinoma of colon with metastases	..	..	..	..	..	..	..
26	75	M	Carcinoma of rectosigmoid with metastases; atrophic gastritis	+	..	..	..	..	..	..
27	76	M	Bronchopneumonia	..	..	..	..	..	..	..
28	77	M	Carcinoma of sigmoid with metastases	..	..	..	..	..	..	..
29	84	F	Arteriosclerotic heart disease; bronchopneumonia; atrophic gastritis	..	..	..	..	..	..	..
30	90	..	Arteriosclerotic heart disease; nephrosclerosis	..	..	+	..	..	..	..

abnormal nerves were found approximately twice as frequently in the patients with ulcer as in those without ulcer. Since it is generally agreed that gastric hypersecretion plays an essential role in the causation of duodenal ulcer, and since the cephalic phase of gastric secretion can be controlled by section of the vagus nerve, it is logical to assume that lesions of the peripheral portions of the vagus nerves might, in some circumstances, play a part in the physiologic changes that precede the development of duodenal ulcer. This assumption will be materially strengthened if, in a statistically significant series of cases, it can be proved that pathologic changes in the vagus nerves are encountered with consistent greater frequency in patients with duodenal ulcer than in those without ulcer. Assuming, further, that the normal function of a nerve is dependent on the proper transmission of impulses, it is possible that changes in the vagus nerves, such as those observed in some of our cases, may be factors in the development of disorders of structure or function occurring in segments of the alimentary tract under vagal control.

SUMMARY

Systematic microscopic study of supradiaphragmatic portions of the vagus nerves removed at operation and autopsy showed, in a number of instances, a gamut of lesions, including inflammatory cell reaction, myelin degeneration, neurolysis, neuronal atrophy and perineural and intraneural fibrosis and scarring. These changes were found approximately twice as frequently in patients with duodenal ulcer as in patients without ulcer. It is assumed that lesions of the peripheral portions of the vagus nerves might, in some circumstances, play a part in the development of disorders of structure or function occurring in segments of the alimentary tract under vagal control.

SERUM NEURITIS

Report of Two Cases and Brief Review of the Syndrome

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MOST physicians are well aware that anaphylaxis and serum sickness may result from the prophylactic use of serum, but it is not well recognized that a disabling neuritis [1] may also follow. This neuritis comprises a definite syndrome and, if treated properly, has a good prognosis. Since the prophylactic use of various serums is still common, it seems worth while to report 2 cases of tetanus antitoxin neuritis recently encountered within a period of one month at the Mayo Clinic.

REPORT OF CASES

CASE 1.—A white man aged 36 entered the clinic on Jan. 4, 1950, with the chief complaint of inability to lift the right shoulder and arm.

The patient had been apparently well until Oct. 29, 1949, when he incurred a minor pitchfork wound in the right foot. The same day, his family physician administered an injection of tetanus antitoxin just below the deltoid area in the right arm. Five days after the injection, generalized urticaria, arthralgia, generalized aching and fever developed. These symptoms lasted approximately twenty-four hours. The following evening (six days after injection of tetanus antitoxin), severe pain ("like muscles pulling apart") developed in the right shoulder and the right side of the back. The next morning (seven days after the injection of tetanus antitoxin), he noted that he was unable to raise the right arm or to move it backward or forward. The pain persisted a week to ten days and was severe. As the pain subsided, he became aware of an area of hypesthesia in the right deltoid area. About the same time, he noticed paresthesia in the ulnar aspect of the left palm and the flexor aspect of the left forearm. Twenty days after injection of tetanus antitoxin, he noted some atrophy of the muscles of the right shoulder. This had not seemed to change appreciably since first noted. He was not aware of winging of the left scapula until just a few days prior to admission (eight weeks after injection of tetanus antitoxin).

There was no previous history of allergic reaction, and he had had no previous injections of tetanus antitoxin.

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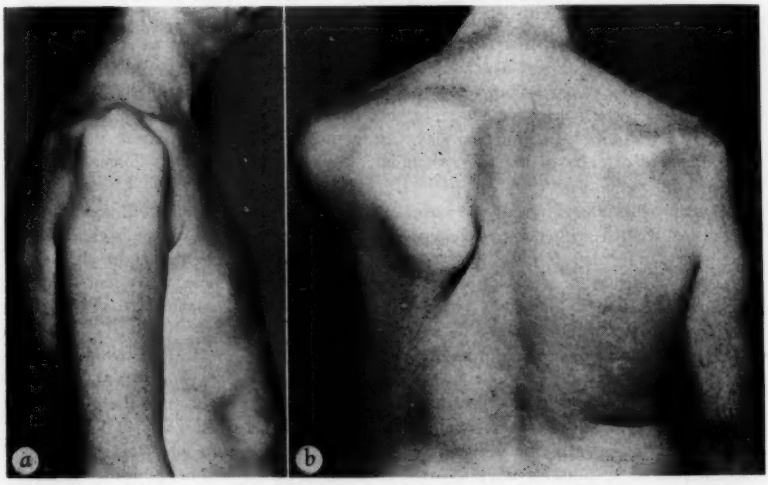
1. The term "serum neuritis" is used here, since it is well established in medical literature. It is recognized that such designations as "serum neuropathy" and "traumatic (compression) neuropathy" would be more correctly descriptive of the condition, as there is little or no evidence that this is an inflammatory condition of nerve tissues.

The treatment which the patient had received before admission consisted of hot baths, diathermy and massage.

The neurologic examination revealed slight weakness and atrophy of the right trapezius muscle. There were marked atrophy of the deltoid, moderate atrophy of the supraspinatus and infraspinatus and slight weakness and atrophy of the serratus anterior, pectoral and triceps muscles on the right side (figure, *a*). On the left, there was moderate weakness of the serratus anterior with definite winging and moderate weakness of the lower fibers of the trapezius (figure, *b*). A few fibrillary twitches were seen in the right deltoid muscle. On the right side there was complete anesthesia in the distribution of the sensory component of the circumflex (axillary) nerve; on the left there was slight impairment of appreciation of light touch and pinprick in the distribution of the circumflex. The activity of the deep reflexes was normal throughout, and the remainder of a complete neurologic examination revealed



Serum neuritis two months after onset (case 1). (*a*) Atrophy of the deltoid, supraspinatus and infraspinatus muscles; (*b*) winging of the left scapula and atrophy of the right trapezius, deltoid, supraspinatus and infraspinatus muscles.

no noteworthy abnormalities. Aside from the neurologic findings, the results of the general examination were within normal limits.

Complete reaction of degeneration was present in the right deltoid muscle, but faradic responses were obtained in all other muscles which were anatomically available for testing in the right upper extremity. An electromyogram of the right deltoid muscle showed numerous fibrillation potentials at rest and no motor unit potentials, either at rest or with effort to contract the muscle. An electromyogram of the right supraspinatus muscle showed no spontaneous motor unit potentials at rest but a reduced number of motor unit potentials during voluntary contraction. The results of routine blood counts, urinalysis and roentgenographic examination of the chest were normal, and the Kline test of the blood for syphilis gave a negative reaction. The sedimentation rate was 4 mm. in one hour. Roentgenograms

of the cervical part of the spinal column revealed rudimentary cervical ribs bilaterally but otherwise showed no abnormality. A roentgenogram of the right shoulder revealed atrophy of the soft tissues but no changes in the bone.

CASE 2.—A white man aged 42 entered the clinic on Dec. 3, 1949, with the chief complaint of weakness of the right shoulder.

On Sept. 10, 1949 he had sustained a nail puncture wound of the left hand. The following day he received an injection of tetanus antitoxin in the upper part of the left arm. He stated that he had been given tetanus antitoxin prophylactically on five previous occasions and had never experienced untoward reactions. Five days after the injection, he noted redness, swelling and itching at the site of the injection; this reaction spread to involve the entire left arm. Seven days after the injection, generalized urticaria, pruritus, nausea, arthralgia and a temperature of 103 F. developed. These symptoms lasted two or three days and were somewhat relieved by orally administered diphenhydramine (benadryl®) and injections of epinephrine. Nine days after the injection, while still having hives, arthralgia and fever, he noted a feeling of fatigue in the right shoulder and difficulty in abducting the right arm. Eleven days after the injection and two days after first noting weakness in the shoulder and arm, he had a gradual onset of severe pain in the upper part of the right arm. This pain continued for approximately one month, gradually subsiding. Pronounced hyperesthesia in the right shoulder was noted for some time after the pain had disappeared. Fourteen days after the injection, the patient noted the beginning of atrophy of the right shoulder. At this time he was no longer able to abduct the right arm.

During the interval from the onset of weakness until December 3, the patient had been treated with hot packs locally and passive exercises of the right upper extremity. He also received five roentgen ray treatments in the right shoulder region. In the last few weeks before his admission to the clinic, there had been a tingling sensation in the right upper arm and some improvement in the strength of the right shoulder and arm.

On neurologic examination, moderate atrophy and weakness of both the supraspinatus and the infraspinatus muscle on the right side were noted. There were conspicuous atrophy and fibrillary twitching of the right deltoid; this muscle could not be moved at all against resistance and only weakly against gravity. The right biceps and triceps muscles did not appear either weak or atrophic, but the deep reflexes of these muscles were greatly reduced in activity. The periosteal reflex of the right radius was normal. No sensory abnormalities were elicited.

The results of routine examinations of the urine and blood, including a Kline test of the blood for syphilis, were within normal limits. Roentgenologic examination of the right shoulder gave normal results. A roentgenogram of the chest showed cardiac enlargement. The patient was known for many years to have had chronic rheumatic endocarditis with mitral valvular defect, which was well compensated. A diagnosis was made of serum radiculitis involving chiefly the fifth and sixth cervical roots on the right.

COMMENT

The usual sequence of events in the syndrome of serum neuritis is as follows: Serum sickness develops approximately three to ten days after the injection of serum. Within a few hours to a few days after the onset of serum sickness, extremely severe pain, usually in the shoulder, occurs, and this is followed within several hours to two

days by weakness of the affected part. The pain at its peak may not be completely relieved even by opiates, but it gradually subsides over a period of several weeks. About this time, in approximately one fourth of cases, numbness will be noted in the area most involved, usually in the distribution of the sensory portion of the circumflex (axillary) nerve.[2] Two to three weeks later local muscular atrophy becomes apparent. The usual course is gradual improvement over a period of four to six months.

Usually the findings conform to a radicular pattern, although cerebral,[3] meningeal,[4] spinal [3] and peripheral nerve [5] lesions have been reported. The commonest site of the flaccid paresis and atrophy which occur is the shoulder. The muscles most frequently involved are the deltoid, the supraspinatus and infraspinatus, the serratus anterior and the trapezius, although the triceps, biceps and pectoral, and even the muscles of the forearm, hand, leg and foot, may be included; those innervated through the fifth and sixth cervical segments comprise the largest percentage reported. The deep reflexes may be reduced, and fasciculations and reaction of degeneration may be present.

Tetanus antitoxin heads the list of serums producing this condition, but the syndrome can be caused also by diphtheria antitoxin, scarlet fever streptococcus antitoxin, antipneumococcus serum, antimeningococcus serum and antistreptococcus serum.[6] In addition, the administration of typhoid vaccine and smallpox vaccine is known to be followed at times by similar neuropathy.[7] Winkelman [7b] has expressed the belief that the neuropathies sometimes seen following the use of sulfonamides and penicillin are identical with the syndrome under discussion. Of 42 cases of serum neuritis cited by Allen,[8] the disease was due to

2. Woltman, H. W.: Neuritis and Other Disease or Injuries of Peripheral Nerves, in Tice, Frederick: Practice of Medicine, Hagerstown, Md., W. F. Prior Company, Inc., 1947, vol. 9, pp. 289-415.

3. Kennedy, F.: Certain Nervous Complications Following the Use of Therapeutic and Prophylactic Sera, Am. J. M. Sc. **177**:555-559 (April) 1929.

4. Bourgignon, G., cited by Doyle, J. B.: Am. J. M. Sc. **185**:484-492 (April) 1933.

5. Robinson, L. J.: Neurologic Complications Following the Administration of Vaccines and Serums: Report of a Case of Peripheral Paralysis Following the Injection of Typhoid Vaccine, New England J. Med. **216**:831-837 (May 13) 1937.

6. Doyle, J. B.: Neurologic Complications of Serum Sickness, Am. J. M. Sc. **185**:484-492 (April) 1933.

7. (*a*) Robinson.[5] (*b*) Winkelman, N. W., Jr.: Peripheral Nerve and Root Disturbances Following Vaccination Against Smallpox: Study of Five Cases, Review of the Literature and Discussion of Related Entities, Arch. Neurol. & Psychiat. **62**:421-438 (Oct.) 1949.

8. Allen, I. M.: The Neurological Complications of Serum Treatment, Lancet **2**:1128-1131 (Nov. 21) 1931.

tetanus antitoxin in 26. Among patients experiencing serum neuritis, there seems to be no significant relation to previous experience with serums. Only 3 patients of 33 cited by Doyle were reported to have had one or more previous injections of tetanus antitoxin.

The most plausible theory of pathogenesis to date is that of urticarial edema of the perineural tissue, with resulting compression neuropathy. The anterior horn cells are probably not significantly involved, since regeneration usually occurs. Kennedy [8] found that the site of paralysis in the case of single long nerves coincided with the site of the greatest incidence of edema from the serum sickness. There is no significant relation between the site of injection of serum and the site of neuritis; in only 3 of 19 of Doyle's cases did the neuritis appear at the same site as that of the injection.[6]

Serum neuritis in the acute phase might be mistaken for acute anterior poliomyelitis, particularly during an epidemic season. The history of a recent injection of serum together with a history of serum sickness with supervening extremely severe pain and weakness is strong evidence in favor of the former. Sensory findings, if present, should help to exclude poliomyelitis, as should the absence of the other systemic manifestations of poliomyelitis. Examination of the cerebrospinal fluid would not always be of aid in this connection, since moderate pleocytosis has been observed in cases of serum neuritis.[9]

The majority of patients gradually recover in approximately six months or as late as eighteen months. About 20 per cent are left with some residual weakness and atrophy, especially of the deltoid muscle.[10]

While intensive treatment probably will not prevent the nerve degeneration from running its course, such therapy will undoubtedly tend to reduce the severity of its side effects, and is therefore indicated. During the acute phase, measures to reduce vasodilation and urticaria (repeated injections of epinephrine, administration of antihistaminics, intravenous injections of hypertonic dextrose solution, sweat packs or artificial hyperpyrexia) are recommended. Afterward, one should attempt to prevent undue stretching of the paretic muscle by its antagonists; this may be achieved by immobilization in a splint. Pending nerve regeneration, muscular tone may be preserved through electrical stimulation, passive exercises and massage.

No preventive measures against this complication of serum therapy are known. It might be presumed that one could obviate the necessity

9. Hogan, B. W.: Neuritis as a Serum Reaction: Report of Two Cases, U. S. Nav. M. Bull. **39**:403-408 (July) 1941.

10. Bennett, A. E.: Horse Serum Neuritis, with Report of Five Cases, J. A. M. A. **112**:590-594 (Feb. 18) 1939.

of using antitoxin by the more widespread use of toxoid; however, even here neuritis may develop, presumably from an allergic reaction to the broth protein of the toxoid.[11] Certainly, if there is a reasonable possibility of wound contamination by tetanus bacilli, tetanus antitoxin should be given, as its benefits are great and the chance of development of neuritis is small. Even with the aid of penicillin, the mortality rate in cases of clinical tetanus is still 17 to 20 per cent.[12]

The 2 cases reported here are typical of serum neuritis. In both cases, chiefly the fifth and sixth cervical nerve roots were affected. In case 1, the presence of paresthesia in the distribution of the sensory component of the left ulnar nerve indicated a more diffuse involvement. The second case is unusual in one respect, namely, that severe neuritic pain did not begin until two days after the onset of weakness; however, even in this case the patient stated that there was a feeling of fatigue in the shoulder at the time of appearance of the weakness. It is interesting that in the second case there was a history of five previous injections of tetanus antitoxin. In the first case the site of injection and the site of neuritis were the same, whereas in the second case they were not.

SUMMARY AND CONCLUSIONS

Two cases of neuritis of the shoulder following injection of tetanus antitoxin are reported. Neuritis should be recognized as a possible complication of the use of serum. The condition may occasionally be confused with acute anterior poliomyelitis, but the historical sequence of serum injection, serum sickness and localized pain and weakness, developing over a period of one to three weeks, in the absence of the usual systemic symptoms and signs of poliomyelitis, should permit the correct diagnosis. In the acute phase, treatment is aimed at reducing allergic edema and pain; later, physical therapy is indicated. The prognosis is usually good; most patients recover in four to six months. The fact that this complication may occur after the use of tetanus antitoxin should by no means discourage its use when indicated, since the complication of neuritis is rare and the benefits from the antitoxin are great.

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11. Wilkinson, S. J.: Multiple Neuritis from Diphtheria Toxoid: Report of Case, J. Pediat. **10**:180-183 (Feb.) 1937. Recently, such a case was encountered at the Mayo Clinic. This occurred five days after the administration of tetanus toxoid and ran a course similar to that of the 2 cases reported here.

12. Diaz-Rivera, R. S.; Deliz, L. R., and Berio-Suárez, J.: Penicillin in Tetanus: A Clinical Analysis of Fifty-Nine Cases, J. A. M. A. **138**:191-194 (Sept. 18) 1948. Colón, E. S.: Tetanus: A Study of Sixty Cases with Special Reference to the Use of Penicillin, Arch. Pediat. **65**:603-607 (Nov.) 1948.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Physiology and Biochemistry

CHANGES IN RENAL FUNCTIONS ASSOCIATED WITH DIABETES INSIPIDUS PRECIPITATED BY ANTERIOR HYPOTHALAMIC LESIONS. C. A. HANDLEY and A. D. KELLER, Am. J. Physiol. **160**: 321 (Feb.) 1950.

Handley and Keller report on the changes in glomerular filtration, renal plasma flow and maximal rate of transfer of dextrose in the renal tubules that occur in diabetes insipidus produced by a large bilateral lesion in the anterior hypothalamus of the dog. It was found that after anatomic destruction of the neurohypophysis without damage to the adenohypophysis glomerular filtration rate, renal plasma flow and maximal rate of transfer of dextrose all decreased 50 per cent or more. These changes were believed to be caused by the inactivation of nephrons with the development of diabetes insipidus.

ALPERS, Philadelphia.

RESPONSE OF THE PARASYMPATHETICALLY DENERVATED CAT'S PUPIL TO ESERINE [PHYSOSTIGMINE]. E. A. NEIDLE, Am. J. Physiol. **160**:474 (March) 1950.

Physostigmine was instilled in the conjunctival sacs of 17 cats in which unilateral or bilateral ciliary ganglionectomy had been performed. Neidle found that the miotic response to physostigmine, which disappears seven to nine days after excision of the ciliary ganglion, returns thirty to sixty days after the operation. After the reappearance of the response to physostigmine, the oculomotor nerve was cut intracranially in 10 cats. There was a complete (1 cat) or partial (9 cats) loss of the miosis due to physostigmine ten days after the operation. Sixty days after the cranial operation the magnitude of the response to physostigmine was of the same order as that present before section of the oculomotor nerve. In 7 cats in which ciliary ganglionectomy had been carried out, no trace of the oculomotor nerves could be found. The response to physostigmine, which was present before the intracranial procedure, was unchanged in the 2 animals which survived the cranial operation.

The return of the pupillary response to physostigmine in cats from which the ciliary ganglion had been excised has been attributed partly to regeneration of preganglionic fibers and partly to other factors.

ALPERS, Philadelphia.

SODIUM PENTOBARBITAL ANESTHESIA AND THE RESPONSE OF THE ADRENAL CORTEX TO STRESS. E. RONZONI, Am. J. Physiol. **160**:499 (March) 1950.

In this study sodium pentobarbital was employed to block release of epinephrine in rats exposed to the stresses of cold, heat and hemorrhage. A search was made for an explanation of the observed variations in the amount of ascorbic acid disappearing from the adrenal glands of anesthetized rats exposed to cold.

Ronzoni found that normal or lightly anesthetized animals exposed to cold ($+5 \pm 1$ C. for one hour or -7 ± 1 C. for twenty minutes) show a decrease in ascorbic acid in the adrenal glands at the end of an hour. Although normal animals showed an increase in blood glucose, lightly anesthetized animals did not. Deeply anesthetized animals showed neither an increase in blood sugar nor a

fall in ascorbic acid of the adrenal glands. With hemorrhage or heat as the form of stress, anesthetic sufficient to prevent the normally observed increase in blood glucose failed to influence the lowering of ascorbic acid in the adrenal glands. Apparently, even light anesthesia is sufficient to inhibit release of epinephrine due to this mild form of stimulation.

These results are incompatible with the hypothesis that epinephrine is essential to stimulation of release of adrenocorticotropic hormone, and they suggest that the elevated metabolic rate is important.

ALPERS, Philadelphia.

EFFECT OF CERTAIN LESIONS OF THE BRAIN ON ELECTROENCEPHALOGRAPHIC WAVE PATTERNS. C. B. COURVILLE, Bull. Los Angeles Neurol. Soc. **14**:119 (Sept.) 1949.

This preliminary study, based on 70 cases of lesions of the brain (46 verified by necropsy and 24 at operation), was undertaken for the purpose of recording what appear to be several electroencephalographic phenomena, with their possible explanation.

The localization of cerebral lesions by electroencephalography is based on the principle of local disturbances in wave pattern incident to the effect of the lesion on the regional cortex. Localizing phenomena consist not only in the occurrence of the usual delta waves and phase reversal activity, but also in the appearance of variations in frequency and amplitude of generally normal waves, the superimposition of frequencies, the production of abnormal wave sequences and quiescence or suppression of normal patterns.

From these studies, Courville concludes that precise localization of cerebral dysrhythmias, particularly if verified by repeated examinations, suggests a persistent latent, but nonprogressive, lesion, i. e., a scar. Regional dysrhythmias, on the other hand, favor the diagnosis of a provocative lesion, most likely an abscess or a benign glioma. The more widespread the dysrhythmia, the more active is the growth or expansion of the lesion.

Distant aberrations in the wave pattern, as found in expanding cerebral lesions, are to be accounted for on the basis of circulatory and structural reactions to the lesion, such as gliosis and edema, the effects of distortion and dislocation of the brain mass, the degree and acuteness of distention of the ventricular system and the distant effects of pressure or transmission of normal potentials by way of the commissural or association systems.

The interpretation of any very widespread variation from the normal electroencephalographic pattern must be given careful consideration, and the possible effects of coma, hydrocephalus and multiple lesions or the considerable effects of malignant tumors must all be evaluated.

The author calls attention to the necessity of repeated electroencephalographic examinations in the presence of suspected focal lesions of the brain, because of the frequent, and even rapid, changes in the electroencephalogram which occur even in slowly progressive and benign lesions. A knowledge of the reactions of nerve tissues to focal lesions, especially to the mechanical effects of expanding lesions, is helpful in the interpretation of electroencephalograms. The wide variation in the responses to similar lesions in identical situations, though still not well understood, may be due to differences in local circulatory reactions.

ALPERS, Philadelphia.

EXPERIMENTAL STUDIES IN POST-TRAUMATIC EPILEPSY. J. RANSOHOFF and S. CARTER, J. Neuropath. & Exper. Neurol. **8**:446 (Oct.) 1949.

Ransohoff and Carter report the effect of experimentally produced, standard cortical scars on the previously established threshold of electrically induced convulsions and on the degree of protection afforded these scarred animals by the commonly employed anticonvulsant drugs.

They found that in cats a small cortical scar in an electrically excitable area causes a significant lowering of the threshold for electrically induced convulsions. The effectiveness of diphenylhydantoin sodium and phenobarbital in raising the threshold of electrically induced convulsions in the animals with cortical scars is the same as it is in normal animals. Their results indicate that the protection of anticonvulsant drugs, such as phenobarbital and diphenylhydantoin sodium, against electrically induced convulsions is as effective in animals with cerebral damage as in normal animals.

ALPERS, Philadelphia.

ELECTRONARCOSIS: III. INHIBITION OF CORTICAL ELECTRICAL ACTIVITY FOLLOWING LOCAL APPLICATION OF PULSED STIMULUS. T. GUALTIEROTTI, E. MARTINI and A. MARZORATI, J. Neurophysiol. **13**: 5 (Jan.) 1950.

The application of a pulsed stimulus directly to the motor cortex alters the electrical activity of the cortex, the most important phenomenon being the inhibition of such activity.

In the anterior part of the occipital lobe, after stimulation of the homolateral motor cortex, the same electrical signs are seen as in the contralateral motor cortex, the wave potentials being out of phase.

Stimulation of the anterior frontal area is without effect on its electrical activity: When the stimulation is applied to the motor cortex, the normal alpha waves increase in amplitude. This increase of the slow rhythm may be due to a functional isolation of the frontal cortex, to which impulses from the motor area are interrupted because of the inhibition.

KELLY, Philadelphia.

INTEGRATION, THEN AND NOW. E. G. T. LIDDELL, J. Neurol., Neurosurg. & Psychiat. **12**:81 (May) 1949.

Liddell discusses the concept of the integrative action of the nervous system, which was first introduced by Sherrington in his studies of the scratch reflex, followed by more modern methods of electric stimulation. The author refers to the phenomena of after-discharge, compounding of reflexes and readiness for integration. He emphasizes particularly the role of the long nerve paths in multicellular organisms and points out the need for further elucidation of their complex functions.

N. MALAMUD, San Francisco.

ELECTROMYOGRAPHY IN MUSCULAR DYSTROPHIES: DIFFERENTIATION BETWEEN DYSTROPHIES AND CHRONIC LOWER MOTOR NEURONE LESIONS. ERIC KUGELBERG, J. Neurol., Neurosurg. & Psychiat. **12**:129 (May) 1949.

Kugelberg discusses the differences obtained in electromyographic recordings between the dystrophic group of muscular disturbances and the atrophic, lower motor neuron disturbances. Eight cases of the proximal type and 8 cases of the distal type of muscular dystrophies were compared with 142 cases of chronic motor neuron disorders. The dystrophies as a group showed that the distribution curve for the duration of the action potentials was shifted toward the short side,

the mean of the durations showed a significant decrease and the relative number of action potentials with a duration of less than three milliseconds had increased. There was also an increase in the polycyclic action potentials, which usually had a shorter duration than in normal muscles, and the amplitude of spikes was decreased. There was a reduction in the number of spikes in cases of advanced disease, indicating patchy distribution in the muscle. The strength represented by action potentials of one to three milliseconds' duration in dystrophic disorders was greatly reduced. On the other hand, in chronic lesions of the lower motor neuron spontaneous fibrillations tended to occur. The action potentials showed greater duration and larger amplitude; polycyclic potentials tended to occur which were usually of longer duration than the average action potentials of normal muscle. The number of spikes was more or less reduced in proportion to the muscular weakness. In the opinion of the author, electromyography facilitates a reliable differential diagnosis of the two types of muscular disorders.

N. MALAMUD, San Francisco.

SITE OF ACTION OF MYANESIN (MEPHENESIN, TOLSEROL) IN THE CENTRAL NERVOUS SYSTEM. BIRGER R. KAADA, J. Neurophysiol. **13**:89 (Jan.) 1950.

The site of action of mephenesin (myanesin®) on the central nervous system was studied in cats and monkeys.

With therapeutic doses of the drug (10 to 40 mg. per kilogram given intravenously), the spinal monosynaptic and multisynaptic reflex discharges, as well as the knee jerk and flexion and crossed extension reflexes, were unaffected. With an increased dose, the multisynaptic reflex discharges were depressed before the monosynaptic ones. Correspondingly, the flexion and crossed extension reflexes were found more susceptible to the drug than the patellar reflex. In accordance with earlier observations, it was found that hyperactive spinal reflexes (produced with light chloralose anesthesia or by injection of strychnine) were promptly reduced to normal with clinical doses of mephenesin. The great enhancement of the multineuron discharge following the injection of strychnine could also be effectively counteracted with mephenesin. Facilitation and inhibition of the knee jerk from stimulation of the reticular formation of the brain stem were reduced or abolished by mephenesin in amounts of 20 to 30 mg. per kilogram. The stimulus threshold for obtaining these effects was measured before and after administration of the drug. In most experiments the two systems were about equally depressed, while in some preparations with very hyperactive reflexes facilitation was somewhat more reduced than inhibition. Similar facilitation and inhibition obtained from the anterior lobe of the cerebellum were reduced with smaller doses of mephenesin (10 to 20 mg. per kilogram). Cortically induced movements were reduced by doses of 15 to 35 mg. per kilogram. Spontaneous cortical and subcortical potentials were unaffected by clinical doses of mephenesin. The repetitive discharges of the cortical potentials evoked were abolished with smaller doses of the drug than was the primary complex. Cortical after-discharge in animals under chloralose anesthesia was reduced.

It is concluded that the more complex multisynaptic pathways are particularly vulnerable to mephenesin. Such pathways are presumably involved in disorders which respond to the drug, such as spasticity, rigidity, certain involuntary movements, petit mal epilepsy and, possibly, certain types of pain.

KELLY, Philadelphia.

ACTION OF CONDENSED ALKYL PHOSPHATES ON THE NERVE-MUSCLE PREPARATION AND THE CENTRAL NERVOUS SYSTEM OF THE CAT. MARY CHENNELLS, W. F. FLOYD and SAMSON WRIGHT, J. Physiol. **108**:375, 1949.

Hexaethyltetraphosphate and tetraethylpyrophosphate potentiate the mechanical response of the nerve-muscle preparation in the cat to single motor volleys. With the use of belly-tendon leads, the record of the electrical response is characteristically modified by the addition, after the initial diphasic wave, of further waves, referred to by the authors as "peripheral after-discharge"; these waves may be repeated for a period of up to one second. The electrical changes are described in detail. The effects of hexaethyltetraphosphate and tetraethylpyrophosphate on the response to repetitive stimulation at frequencies of 10 to 50 per second are more complex. The outstanding feature of the electrical response is the disappearance of the peripheral after-discharge after the first few responses. Hexaethyltetraphosphate and tetraethylpyrophosphate antagonize the peripheral action of curare on the nerve-muscle preparation. Curare, injected after potentiation has been produced by these two drugs, rapidly extinguishes the peripheral after-discharge to single motor nerve volleys. The characteristic effects of hexaethyltetraphosphate and tetraethylpyrophosphate on the nerve-muscle response are abolished after chronic motor denervation of the muscle. Hexaethyltetraphosphate and tetraethylpyrophosphate facilitate various reflexes (knee jerk; flexor, peroneus, crossed extensor and jar reflexes) and induce convulsions. Central after-discharge is enhanced and prolonged. The effects described are independent of changes in the nerve-muscle response or in circulation and respiration and are due to direct action on the central nervous system. The central actions are obtained on intravenous and intrathecal injection in animals under chloral-dextrose anesthesia, decerebrated animals and animals after section of the spinal cord. Attention is drawn to the similarity in the central action of the condensed alkyl phosphates to that of physostigmine and the tertiary carbamic ester anticholinesterases, and to that of di-isopropyl fluorophosphonate. The peripheral neuromuscular action of hexaethyltetraphosphate and tetraethylpyrophosphate can be confidently attributed to their anticholinesterase action. The mechanism of the central excitant action cannot yet with certainty be ascribed to this property of the drugs.

THOMAS, Philadelphia.

ACTION OF BOTULINUM TOXIN ON THE NEURO-MUSCULAR JUNCTION. A. S. V. BURGEN, F. DICKENS and L. J. ZATMAN, J. Physiol. **109**:10, 1949.

The toxin of Clostridium botulinum produces irreversible paralysis of the isolated rat phrenic nerve–diaphragm preparation, owing to neuromuscular block. Conduction in the nerve is unaffected, and the muscle responds normally to direct stimulation. The neuromuscular block produced by toxin differs from that of curare in that motor-nerve tetani are well maintained, the summation curve for the two stimuli is normal and the paralysis is unaffected by physostigmine, neostigmine, tetraethylpyrophosphate, potassium chloride or epinephrine; the motor end plates remain sensitive to acetylcholine and the output of acetylcholine on motor-nerve stimulation is greatly reduced. It is assumed that any effect of the toxin on the motor nerve must occur after it has lost its medullary sheath on entering the end plate. By an irreversible fixation of the toxin to the fine nerve fibers, transmission of the impulse through them is abolished; consequently, no release of acetylcholine takes place, with resulting neuromuscular block, as observed.

THOMAS, Philadelphia.

RECOVERY OF STRETCH REFLEXES AFTER NERVE INJURY. D. BARKER and J. Z. YOUNG, Lancet **1**:704 (May 24) 1947.

Barker and Young studied the recovery of proprioceptive function in the crushed nerves of rabbits, using the stretch reflex or the knee jerk as a test. They devised a means of measuring the degree of movement of the leg, when the patellar ligament is struck, from the horizontal position upward. This determination entails an "inertia factor," which is the force that the quadriceps muscle must exert to lift the weight of the shank and foot in order to produce a just perceptible upward movement. They compensated for this by interrupting only the lateral and central branches of the crural nerve, leaving the medial branch intact. The recovery of the other muscles was watched by noting any increase in response. This determination was complicated, however, by hypertrophy of the intact muscle, which reached a maximum twenty to thirty days after operation. In spite of this, the following results were noted: In about thirty days, the proximal parts, and in fifty days the distal parts, began to contract. This regeneration continued until the preoperative level was reached; then occurred a supernormal phase, due to hypertrophy of the muscle, and, finally, a decline to the normal level. This took place over a period of about one hundred and ten days. To prove that the reinnervation was complete, the previously intact nerve was crushed after several hundred days, when the response decreased proportionately. In experiments in which all three branches of the nerve were crushed, a response could first be detected in forty to forty-five days, and the return to a normal level was rapid thereafter, usually in about ten days. Cutting and suturing the nerves gave varying degrees of recovery, ranging from 19 to 70 per cent, and the recovery seemed to be correlated with the closeness of union of the severed stumps. Histologic studies of the muscle spindles have not been completed.

MADOW, Philadelphia.

ELECTROENCEPHALOGRAPHIC STUDY OF SENSORY DOMINANCE OF ONE CEREBRAL HEMISPHERE. L. CORNIL and H. GASTAUT, Presse méd. **55**:421 (June 21) 1947.

Cornil and Gastaut studied the encephalograms of 120 adults and of 30 children between the ages of 5 and 12 years with regard to the sensory dominance of one of the cerebral hemispheres. More than 50 per cent of the normal persons presented asymmetry in the amplitude of the alpha rhythm, and the less ample rhythm was always located opposite the half of the body used with preference, i. e., on the side of the dominant hemisphere. Blocking of the alpha rhythm by opening the eyes or by performing mental arithmetic caused a more complete attenuation of the alpha rhythm on the same side. Rhythmic potential waves in the occipital region induced by intermittent rhythmic lighting of the retina were often asymmetric, and the largest amplitude was always obtained on the side which at rest showed the less pronounced amplitude; the rhythm was in general of larger amplitude and was more regular and more rhythmic in the dominant hemisphere than in the dominated one. It is suggested that there is a richer conveyance of sensory, particularly of visual, messages on the side of the dominant hemisphere. The dominant cerebral hemisphere (the left side in right-handed persons) "receives" more sensory messages, while it "conveys" more motor signals than the opposite side. The reaction of blocking the alpha rhythm, which in the course of mental effort is more important in the dominant hemisphere, proves that this hemisphere plays a predominant part in the process of application of the mind, and probably in other processes of psychic life.

J. A. M. A.

Diseases of the Brain

TICK PARALYSIS: REPORT OF A CASE IN PHILADELPHIA. K. E. DAWSON, A. J. SHERMAN and A. C. LABOCCETTA, Am. J. Dis. Child. **79**:491 (March) 1950.

It is important that the epidemiologic aspects of tick paralysis be known, and since no cases had been reported from Pennsylvania, the present case of tick paralysis in Philadelphia was recorded. This case is the sixteenth reported east of the Mississippi River and the second north of the Mason-Dixon line. The case is atypical in that, although progression of the disease had occurred to the point of extreme generalized muscular weakness and the appearance of facial paralysis, there was no increase in the severity of the symptoms and signs after the first forty-eight hours of the illness; in fact, there were slight but definite improvement in the facial paralysis and diminution in the degree of ataxia before discovery of the tick. Rapid recovery, however, did not occur until the tick had been removed. This suggests that the syndrome caused by the bite of Dermacentor variabilis Say (here involved) is less severe than that caused by the bite of Dermacentor andersoni Stiles.

The authors emphasize the importance of prompt diagnosis.

ALPERS, Philadelphia.

SULFADIAZINE NEPHROSIS WITH HYPERCHLOREMIA AND ENCEPHALOPATHY. W. T. GOODALE and T. D. KINNEY, Ann. Int. Med. **31**:1118 (Dec.) 1949.

Goodale and Kinney report a fatal case of toxic nephrosis with hyperchloremia and encephalopathy following the oral administration of only 4 Gm. of sulfadiazine. The rapid death, with a cerebral type of hyperpyrexia and shock, without evidence of cardiac failure or edema, suggests that the encephalopathy may have been a major cause of death.

The authors briefly review the work of Luetscher and Blockman, who described a peculiar syndrome of hyperchloremia and encephalopathy occurring with toxic nephrosis after sulfathiazole therapy. The hyperchloremia and encephalopathy may have been the major cause of death in at least 2 of their 5 cases, rather than the uremia or any other complication.

The authors point out, again, the potential dangers of sulfonamide therapy, even in small oral doses, and the ineffectiveness of the routine administration of alkalis in preventing a fatal nephrosis due to the drug.

Since this report was completed, 2 additional cases of hyperchloremia and hypernatremia without a high degree of acidosis have been observed. Both cases showed a toxic encephalopathy. In 1 case the condition followed the use of sulfathiazole.

ALPERS, Philadelphia.

ANALYSIS OF ELECTROENCEPHALOGRAPHIC FINDINGS IN FORTY CASES OF VERIFIED BRAIN TUMOR: III. ELECTROENCEPHALOGRAPHIC FINDINGS IN METASTATIC TUMORS OF THE BRAIN. HENRY M. CUNEO, CARL W. RAND and H. SJAARDEMA, Bull. Los Angeles Neurol. Soc. **14**:149 (Sept.) 1949.

The authors report on the clinical, pathologic and electroencephalographic findings in a series of 7 cases of metastatic tumor.

In case 1, with five metastatic bronchogenic carcinomas present in the brain, only one was correctly localized and removed surgically. The encephalogram was also confusing in that only one of the other four tumors was even suspected. In

case 2 an undifferentiated carcinoma in the right occipital lobe was not localized by electroencephalogram. In case 3 a mucoepithelial tumor of the left sphenoidal ridge was lateralized but not localized by electroencephalogram. In case 4 a metastatic carcinoma with a large cystic cavity was present in the left parieto-frontal area. The electroencephalogram did not give definite localization. It is difficult to understand why the electrical disturbance recorded was so minimal in this case, with a good-sized tumor and a large cyst. In case 5, one of multiple metastatic melanomas of the brain, the encephalogram was severely disturbed. While at the time the electroencephalographic study was made the authors did not dare to localize any distinct focus, in retrospect it was seen that the reported phase reversals corresponded accurately with the four tumors described at autopsy. In case 6 a metastatic bronchogenic carcinoma involved the left lateral ventricle, and the lesion was accurately localized by electroencephalogram. This was the only tumor in the series that had invaded a lateral ventricle. In case 7 a metastatic bronchogenic carcinoma in the right motor area was correctly localized by electroencephalogram. This tumor was difficult to localize. The abnormalities were slight and confined to a small area, and the phase reversal was not clear at any time. It is confusing that in the presence of a well circumscribed tumor such a slight abnormality was present.

ALPERS, Philadelphia.

ELECTROENCEPHALOGRAPHIC FINDINGS IN SUBDURAL HEMORRHAGE AND HEMATOMA: REVIEW OF THE LITERATURE AND REPORT OF THIRTEEN CASES. C. MARSH, G. D. HJARTARSON and C. B. COURVILLE, Bull. Los Angeles Neurol. Soc. **14**:163 (Sept.) 1949.

In this study, Marsh and collaborators record their observations in 13 cases of verified subdural hemorrhage and hematoma. From their findings, they are in agreement with other observers that considerable variation occurs in cases of subdural hematoma. Previously stated postulates that subdural hematomas produce "amplitude asymmetries" or "silent areas" due to an interference by the lesion with conduction of potentials to the overlying scalp are not confirmed by their observations. Rather, their observations favor the concept that suppression of alpha activity is usually due to depression of the pacemaker in the parieto-occipital region.

On this basis, posteriorly located subdural hematomas are apt to result in suppression of alpha activity (at times with partial replacement with delta waves), while anteriorly situated lesions are not. Suppression, therefore, may be helpful not only as a diagnostic factor but in suggesting the point of making the burr hole for adequate drainage. Because of the variability in the electroencephalographic tracing, this method cannot be relied on entirely in establishing the correct diagnosis, at least at present.

This series of 13 cases include 1 case of subdural neomembrane, 1 case with a neomembrane on one side and a hematoma on the other, 1 case with a hematoma on one side and a hygroma on the other, 3 cases with a bilateral subdural hematoma and 7 cases with a unilateral subdural hematoma.

Of the 9 cases of unilateral lesions, correct lateralization was possible on the basis of electroencephalographic findings in 6 (in 4 with ipsilateral dysrhythmia, in 1 with ipsilateral suppression characterized by "amplitude asymmetry" and in 1 with bilateral dysrhythmia but with predominant ipsilateral alterations). In 2 cases lateralization was incorrect due to suppression of alpha activity on the side opposite the hematoma. In 1 case generalized dysrhythmia without hemispheral predominance made lateralization impossible. Of 4 cases of bilateral lesions, the

larger lesion was correctly lateralized in 3 instances by the occurrence of suppression. In 1 case with generalized dysrhythmia the hemispheral predominance was present on one side, although the two lesions contained about the same amount of fluid.

Factors other than suppression, i. e., transmission of abnormal potentials through the commissural or association bundles, distortions and dislocations of the brain, including dilation of the contralateral ventricle, and counterpressure, accounted for the misleading lateralizing and localizing phenomena. ALPERS, Philadelphia.

PARKINSONISM AND PREGNANCY: THE INFLUENCE OF PRESUMED SUBCLINICAL ENCEPHALITIS IN THE PRODUCTION OF THE CLINICAL SYNDROME, H. E. ANDRÉN, Bull. Los Angeles Neurol. Soc. **14**:193 (Dec.) 1949.

This study is concerned with a small number of cases in which parkinsonism develops during pregnancy or the puerperium without previous history of encephalitis or other etiologic factors. It is the author's belief that the condition probably stems from a previous subclinical episode of encephalitis.

A survey of the cases reported in the literature makes it clear that parkinsonism follows encephalitis during pregnancy in a high percentage of cases. Therefore there is some factor of pregnancy which renders the corpus striatum more susceptible to the virus or toxin of encephalitis.

The parkinsonian syndrome (*a*) may develop shortly after the encephalitis but during the same pregnancy, (*b*) may occur during a subsequent pregnancy with one or more normal pregnancies interposed or (*c*) may be exaggerated by subsequent pregnancies. Pregnancy, therefore, may be the factor which reactivates the virus or toxin of encephalitis. ALPERS, Philadelphia.

PINEALOMA WITH A SOLITARY SPINAL METASTASIS. FRANK R. MAGAREY and H. R. I. WOLFE, J. Neurol., Neurosurg. & Psychiat. **12**:155 (May) 1949.

Magarey and Wolfe report a case of pinealoma with solitary metastasis to the cervical region of the cord. The metastatic tumor was a dumbbell type, causing symptoms of compression of the spinal cord, for which a laminectomy was performed. The primary tumor gave no clinical signs or symptoms, and the correct diagnosis was made only at necropsy. The authors emphasize the uniqueness of their case. N. MALAMUD, San Francisco.

THE TONIC PUPIL. G. S. GRAVESON, J. Neurol., Neurosurg. & Psychiat. **12**:219 (Aug.) 1949.

Graveson studied 15 patients with tonic pupils, 12 of whom were females and 3 males, their ages varying from 12 to 55 years. Eleven were originally seen because of pupillary inequality, and the remaining 4 patients, because of blurring of vision with or without headache. In all cases the Wassermann reaction of the blood was negative. In questionable cases the Wassermann reaction of the cerebrospinal fluid was determined, and it also proved to be negative. Of the 15 patients, 12 had absence of one or more tendon reflexes. Two types of pupillary reaction can be distinguished: the "fixed" and the "ordinary." The "fixed" type is less common and is unilateral, one pupil being larger than normal, irregular in shape and totally unresponsive to light or in convergence. In tests of the accommodation mechanism, this type may show slow contraction or, less often,

relaxation. In some instances such pupils may contract under the influence of a 2.5 per cent solution of methacholine (mecholyl®) which in this concentration does not ordinarily affect the normal pupil. The "ordinary" type may be unilateral or bilateral, the pupil being irregular in shape, of any size and often placed eccentrically in the iris. The essential reaction is slowness of dilation after convergence. Because of the wide variation of the pupillary reactions, the author suggests this classification in preference to Adie's division into typical and atypical phases. Thus, the only typical features are the irregularity of the pupil and the slowness of relaxation after convergence. While in neurosyphilis the pupil shows a similar sluggish contraction, on convergence the subsequent dilation is normal, whereas in the tonic pupil it is always delayed. While in certain instances the tonic pupil can be ascribed to a specific infectious or traumatic process, in the vast majority of cases it is of of unknown origin and is usually considered benign. The author states his belief that the lesion is probably at the efferent end of the pupillary reflex pathway, but he concedes that this opinion is speculative because of inadequate knowledge of the pupillary reflex pathways.

N. MALAMUD, San Francisco.

ABDOMINAL EPILEPSY. M. T. MOORE, Rev. Gastroenterol. **15**:381 (May) 1948.

Moore reports 3 cases of abdominal epilepsy with paroxysmal abdominal pain and disturbed motility of the gastrointestinal tract (2 women aged 50 and 32 respectively and a boy aged 12) in which a satisfactory response to anticonvulsant therapy was obtained. Each case satisfied either all or most of the following criteria necessary to establish the diagnosis of abdominal epilepsy: 1. The patients must be examined by all available methods to rule out intrinsic disease of the pelvic, abdominal and thoracic viscera, morbid involvement of the spinal cord or peripheral nerves and psychosomatic projection mechanisms. 2. Historical data regarding the possible existence of cerebral disease or dysfunction should be uncovered. 3. The behavioristic occurrence of the pain should adhere to the pattern of epilepsy. 4. The presence of associated epileptic phenomena, either prior to or during the episodes of abdominal pain, must form corroborative evidence of the nature of the disorder. 5. Positive neurologic signs and results of laboratory studies, including cytologic and chemical tests, roentgenologic studies of the skull and electroencephalographic recordings, indicating the existence of a cerebral structural or physiologic disorder, should be in evidence. 6. Favorable effects of anticonvulsant drugs on the occurrence of abdomnial pain and/or abnormal gastrointestinal motility should be exhibited, and the influence of these drugs on the electroencephalogram should in most instances parallel the clinical results. Absence of abnormal cerebral activity, as observed in the eletroencephalogram, may be encountered in patients with abdominal epilepsy, as in epilepsy of all types.

J. A. M. A.

SOME NEUROLOGICAL ASPECTS OF THE HUNGERWINTER IN HOLLAND. F. E. POSTHUMUS MEYJES, Folia psychiat., neurol. et neurochir. **51**:257 (Aug.) 1948.

The winter of 1944-1945 is referred to in the Netherlands as the "hungerwinter" (October 1944 to May 1945). In a famine of seven months' duration, no increase in the incidence of major neuropathies was observed, in contrast to that in civilian and military prison camps in the Netherland Indies and in Japan. The reason for the failure of neuropathies to develop is attributed to the low carbohydrate ration with relatively high thiamine (vitamin B_1) value, the low outside temperature, the low metabolic rate and the lack of hard labor, factors which reduced the demand of the tissues for thiamine.

ALPERS, Philadelphia.

Society Transactions

PHILADELPHIA NEUROLOGICAL SOCIETY AND NEW YORK NEUROLOGICAL SOCIETY

Sherman F. Gilpin Jr., M.D., and Samuel Brock, M.D., *Presiding*

Joint Meeting, April 23, 1948

A Case of Amyotonia Congenita Associated with Bilateral Subdural Hygroma and Occlusion of the Sagittal Sinus: Demonstration of Occlusion by Diodrast Sinography. DR. MICHAEL SCOTT, Philadelphia.

Amyotonia congenita was first described by Oppenheim in 1900. Most of the autopsy reports have centered on the pathologic changes in the muscles and the anterior horn cells of the spinal cord, and little attention has been paid to the changes in the cerebrum. Recently Burdick, Freeman and others have reported a conspicuous absence of Betz cells in the paracentral lobule, but they suggested no cause for this abnormality.

The author presented a case of amyotonia congenita showing the classic biopsy changes in the muscles of the extremities. In addition, the patient had marked bilateral subdural hygroma, with increase in the protein content of the subdural fluid.

The sagittal sinus had become occluded in utero as the result either of infection or of a congenital factor. This prevented the proper drainage of the cortical veins in the region of the paracentral lobule and the proper absorption of the subarachnoid fluid and resulted in impairment in development, histologically and cytologically, of the paracentral lobule. This, in turn, resulted in the lack of proper stimulus to the anterior horn cells in the spinal cord supplied by the paracentral lobule and, finally, was reflected in the fetal and abnormal development of the muscle cells, particularly of the lower extremities and partially of the upper extremities. The subdural hygroma was an additional, and secondary, factor in the production of the symptoms.

It was the author's belief that all cases of amyotonia congenita should be carefully studied for the presence of subdural hygroma and occlusion of the sagittal sinus.

DISCUSSION

DR. SAMUEL BROCK, New York: I am not prepared to discuss this paper, for I have no neuropathologic experience. I should like to hand the task over to Dr. Freeman, who has the requisite knowledge of neuropathology.

I can only praise this case study, for it represents an adventurous attitude toward a disease which neurologists have taken too much as a matter of fact. It may well open a new chapter in the etiology of the condition.

DR. WALTER FREEMAN, Washington, D. C.: Dr. Scott's idea that the development of the cortex influences the development of the anterior horn cells in the spinal cord is little short of fantastic. The spinal cord is in a fairly high state of development at the time the cortex is scarcely more than an aggregation of cells. I have examined 4 cases of amyotonia congenita—in fact, I had a fifth one later—and in all of these there was an open longitudinal sinus.

Probably what occurred in the case was a combination of the two conditions, for there is no question that amyotonia congenita was present in this case. It

happened to be complicated by thrombosis of the sagittal sinus, in whatever way the latter occurred. One sees cases of this sort in which the lower limbs are withered, but the paralysis is apt to be of a spastic variety, rather than the flaccid type found in this case.

DR. MICHAEL SCOTT, Philadelphia: It was not my intention to suggest that an occlusion of the sagittal sinus was the only cause of amyotonia congenita. I tried to show that occlusion did occur in 1 case and was perhaps an etiologic factor. Incidentally, many of Dr. Freeman's case reports were based on an examination of brains that were sent him, and no mention was made that the sagittal sinus had ever been examined.

The important point that I wish to make is that a complete autopsy should be performed in cases of this type and a positive statement made concerning the patency of the dural venous sinuses and the presence or absence of a subdural membrane.

Observations on the Effect of Myanesin. DR. GEORGE D. GAMMON and DR. J. A. CHURCHILL, Philadelphia (by invitation).

Mephenesin (myanesin®; 3-ortho-toloxy-1, 2-propanediol) has been shown to cause profound muscular relaxation in animals, with no loss of consciousness. Analgesia, ataxia and complete paralysis result from higher doses. The effects of mephenesin were investigated on various pathologic states.

The tremor was abolished in 7 cases of parkinsonism, and choreoathetotic movements were reduced or abolished in 4 cases. Rigidity was reduced without the strength being affected.

Senile tremor was improved. Chorea was not altered, and the intention tremor of multiple sclerosis was increased. The spasms of tetanus were eliminated.

Spontaneous pain and exaggerated response to pinprick were reduced in a patient with tabes. Causalgic pain was reduced for twenty-four hours, but phantom limb pain was not altered.

Since petit mal discharges may originate in the thalamic or the subthalamic nuclei, patients with petit mal were given mephenesin as a test of the possibility that abnormal discharges from the thalamus or associated structures might be affected by the drug. The petit mal discharges were abolished in 6 cases. Convulsions associated with pathologic changes in the cortex were not affected.

Three psychotic patients showed improvement during the time that the drug was active. One was a deteriorated schizophrenic patient; the second had a reactive depression, and the third was an unresponsive agitated patient.

It would appear that the drug in moderate doses acts selectively on the subcortical nuclei in the basal ganglia, the thalamus and the brain stem. With larger doses, both motor and sensory conducting mechanisms in the spinal cord are blocked, and the cerebral cortex is depressed. Ultimately, a peripheral neuron block is produced. In pathologic cases, any prolonged, repetitious or grouped discharge is reduced by mephenesin.

This paper was published in the February 1949 issue of the *American Journal of Medical Sciences,* page 143.

DISCUSSION

DR. E. B. SCHLESINGER, New York (by invitation): Our experiences with mephenesin parallel those of Drs. Gammon and Churchill in most respects (Schlesinger, E. B.; Drew, A. L., and Wood, B.: Clinical Studies in Use of Myanesin, *Am. J. Med.* **4**:365 [March] 1948). I might mention some of these experiences. In our paper we disagreed with Stephen and Chandly (*Canad. M. A. J.* **57**: 463, 1947) on only one significant point. They stated the impression that the drug did not affect spasticity of spinal cord origin but cited many cases of significant effect on spasticity associated with cerebral disease. This differentiation would

be difficult to understand neurologically. Our experience is that spasticity is ameliorated temporarily, whatever its origin. Drs. Stephen and Chandly have visited us, and I believe, we are all in agreement now.

We use mephenesin in many ways. In cases of ruptured cervical or lumbar disk, we use it as a diagnostic and therapeutic aid. After intravenous medication there are often abolition of pain and striking increase in mobility. This may continue for hours or days and start the patient well on the way to a good conservative result, with bed rest, etc. On the other hand, the pain may return in a matter of seconds. In such cases we have found that the nerve root is severely compressed by the lesion, and conservative treatment usually fails. The only relief then is by operation. In other words, if positive muscular relaxation does not reduce the pain and relieve the mechanical compression, traditional measures, such as traction, will fail.

As Dr. Gammon stated, we use the drug a great deal in treatment of the acute low back syndrome, "frozen" shoulder and wryneck and as an aid to skeletal traction. It has a wide margin of safety and affords specific relaxation. Mephenesin has a local anesthetic action, of the order of procaine, so that some of the effect is probably on this basis, rather than due to muscular relaxation.

We also use the drug in analyzing the nature of various neuromuscular mechanisms. For instance, in poliomyelitis there is widely considered to be an entity known as muscle spasm. The patient shows extreme limitation of limb motion, characteristic of the disease; the physical therapists call it "muscle spasm." We give the patient mephenesin to a point at which it would be facetious to use this term, since the muscles can be made to dance about "like little Egypt." Repeated tests of range of motion at this point showed that movements stopped at exactly the same point as they did before. To me, this is evidence that the pain occurred when nerve elements were stretched, as in the Laségue test, in which spinal elements and roots are stretched, with production of severe pain. We were of the impression that the so-called muscle spasm of poliomyelitis was, at least in part, due to a similar mechanism.

Another entity which we have studied is rheumatoid arthritis of the spine (Marie-Strümpell arthritis). It was interesting to find that pain could be abolished immediately and the patient put through a considerable range of motion under the effects of mephenesin; so muscle spasm (secondary to what I do not know) is at least a factor. The next important step is to find out whether the disease later goes on to ankylosis and decalcification as it usually does.

These experiments, though perhaps not of great interest to you, may demonstrate that mephenesin is a fascinating drug to use in analysis of neuromuscular mechanisms, owing to its specific relaxing effect on muscles.

I should like to call attention to an observation in our electromyographic studies. A patient with paralysis agitans, on whom we made electromyographic studies, showed rapid obliteration of rigidity at rest and a considerable reduction on motion after receiving the drug. However, one could still elicit an extremely hyperactive stretch response (or spasticity) underlying the rigidity. As we increased the concentration of the drug, that effect, too, disappeared. This is an excellent demonstration of the fact that the drug affects first the mechanisms of the brain stem (or bombardment of central origin) and only later affects the segmental mechanisms responsible for spasticity.

Unlike Dr. Gammon, we found a pronounced effect on reflex mechanisms and were able to demonstrate disappearance of crossed reflexes, other types of spreading mass reflexes and similar phenomena in cases of severe damage to the spinal cord.

An electromyogram showing the obliteration of rigidity in the muscles of the arm in a case of severe rigidity was shown. Abnormal spikes were blotted out.

After injection of 75 cc. of a 2 per cent solution of mephenesin, the characteristic motor activity at rest was practically gone. The next slide shows that, although there was still some activity on extension of the arm, there was marked reduction of that activity, and theoretically this patient could be given purposeful physical therapy under the effect of the drug.

Another slide, of a spastic limb, showed a much less pronounced effect of the drug. After administration of 100 cc. there was obliteration of abnormal spikes on attempted tests, but this effect was much more difficult to obtain than in the case of tremor and rigidity.

These records are not nearly of the quality of Dr. Gammon's, but they illustrate what a better analog might do if it were effective when taken orally. We have had a case or 2 in which mephenesin was effective when given by mouth. It is worth trying. In the large proportion of cases, however, there is no response on oral administration.

Dr. George D. Gammon: Some of the reported differences in the action of this drug may depend on the dose. In the beginning we did not realize that it was necessary to maintain a constant rate of infusion, after the original dose, in order to maintain the action of the drug. Even the animal experiments showed a differentiation in the effect on higher mechanisms—an initial paralysis and ultimately a neuromuscular block.

The abolition of spasticity of spinal cord origin requires a larger amount of the drug than does abolition of spasticity produced by discharges from the nuclei of the brain stem. We are interested in analyzing the action of this drug not so much because of its immediate therapeutic action as that we might be in a position to study analogs.

Invasive Meningiomas of the Base of the Brain: Report of Three Cases.
Dr. Helena E. Riggs and Dr. Winslow Stratemeier (by invitation).

In general, the meningioma is a well localized growth which involves neural tissue by compression. Globus, however, stated that the leptomeningioma is almost always invasive, infiltrating both the dura and the adjacent portion of the brain. Recently we have encountered 3 cases of this meningioma, all situated at the base, which showed strong invasive tendencies.

Case 1.—In a white woman aged 63, necropsy revealed that the entire right half of the floor of the middle fossa was filled with a poorly defined mass of firm, white tumor tissue which surrounded the sella turcica and compressed the temporal pole laterally. Posteriorly the mass was continuous with the tentorium and spread out over the lateral wall of the posterior fossa, partially filling the tentorial notch, compressing the pons and filling the cerebellopontile angle. The basilar and right vertebral arteries were attached to the tumor.

Case 2.—In a Negro, aged 70, necropsy showed a mass of dense white tissue diffusely covering the entire base of the middle fossa and extending over the cribriform plate anteriorly and the clivus posteriorly. The sella turcica was entirely engulfed. The tumor was freed from the skull by stripping the dura. On the right side, the internal carotid artery; the anterior, middle and posterior cerebral arteries, and the superior cerebellar arteries, with the basilar artery, were incorporated in the tumor. Both optic nerves anterior to the optic foramens appeared swollen. The right temporal lobe was compressed. There was recent anemic necrosis of the subcortical white matter of the frontal region, the anterior limb of the capsule and the caudate nucleus on the right side.

CASE 3.—In a white woman aged 47, necropsy showed a poorly defined, shaggy mass of tissue densely adherent to the dura over the right lateral wall of the posterior fossa and extending over the inferior surface of the tentorium. This filled the cerebellopontile angle and was adherent to the lateral surface of the pons.

Comment.—All these tumors showed a similar histologic picture, with the characteristic whorls of a leptomeningioma of the arachnoid type. The tumor in all cases infiltrated the capsule of the pituitary gland and invaded the gland itself. The internal carotid arteries at the sella turcica were surrounded by tumor, and the gasserian ganglia were compressed. There was invasion of the nerve roots of the gasserian ganglia in case 1. In case 2, the optic nerves anterior to the optic foramens were surrounded by tumor, which lay beneath the dural investment and spread out over the sclera at the entrance of the optic nerves. The sigmoid portion of the lateral sinus was filled with tumor in case 3, and the capillary tufts of the choroid plexus in the angle contained small masses of tumor cells.

DISCUSSION

DR. JOSEPH GLOBUS, New York: Dr. Riggs quoted me as saying that the leptomeningioma, a special type of tumor which duplicates the structure of the soft meninges, is likely to be invasive. I have reason to believe that that statement is correct, and I am, of course, reassured on that point by Dr. Riggs's beautiful demonstration. I believe I can do best by showing a few of my own slides. I think they will fully support the statement made by Dr. Riggs.

Here is a tumor which you will recognize as leptomeningioma. Brain tissue overlies the tumor, and the material has invaded the brain substance. However, the term "invasion" may not be entirely correct, as I believe there is no real invasion. It is, rather, in the nature of an extension, perhaps concurrent with the growth of tumor tissue outside. Dr. Riggs has made an excellent contribution to a subject which was thought to be completely closed. She has reopened it in such a way that it will probably induce others to study meningiomas from that point of view.

DR. LEWIS D. STEVENSON, New York: None of my own material would illustrate this subject nearly as well as the beautiful slides shown by Dr. Riggs. I am happy to have seen the sections on these cases which she sent to me. In my opinion, there is no question about the diagnosis of leptomeningioma. It is interesting to see the invasive quality of these basal meningiomas, which may account for some of the poor surgical results that I have had in my own case.

It is surprising how poor are the results after removal of meningiomas that seem quite simple and fairly well extirpated. Yet there are persisting symptoms and a tendency for these tumors to grow again. That is quite apart from the difficulty attached to the removal at the base of the brain, where the tumor is attached to large vessels, and often the optic nerve.

I should like to show slides from a case I picked up in the medical examiner's autopsy room the other day of a meningioma entirely confined to the lateral ventricle, and apparently growing from elements in the choroid plexus. In the first slide is a fibrous tumor, and the next slide shows it to be a meningioma; at the top one sees the choroid plexus of the lateral ventricle. On the next slide one can see the whorls. I think everyone would call this tumor a meningioma. It is a rather rare type, which Cushing described in his book on meningioma but which is not often encountered. This tumor, as far as I know, was without symptoms. It was about the size of a small hazelnut.

DR. SAMUEL BROCK, New York: May I ask Dr. Riggs if these tumors invade bone? I have been thinking of diagnostic roentgenograms in this situation.

DR. HELENA RIGGS, Philadelphia: No, they are not invasive of bone. In 2 cases there was erosion of the ethmoid cells.

In the last case, in which there was a draining ear, there was complete failure in diagnosis because the roentgenologic diagnosis was chronic mastoiditis and autopsy revealed grossly that the pyramid of the mastoid bone was entirely gone. I think that the pressure from the tumor mass is what causes necrosis of the bone.

Dr. Stevenson, do you want to answer the question?

DR. LEWIS D. STEVENSON, Philadelphia: I am sorry I cannot answer that question because the specimen was given me by the medical examiner simply as a tumor of the choroid plexus. There was no history provided.

Surgical Results with Cerebellar Astrocytomas. DR. FRANCIS C. GRANT, Philadelphia.

From 1924 to 1947, 61 patients with cerebellar astrocytoma were treated in the neurosurgical service of the Hospital of the University of Pennsylvania; 5 of these were operated on at the Graduate Hospital of the University but are included in this series because the operation was performed and the patients followed by the neurosurgical staff of the University Hospital.

Location of Tumor.—Elvidge, Penfield and Cone, in a study of the gliomas, reported 14 cerebellar astrocytomas, 7 of which were midline and 7 hemispheral. They pointed out that "all the midline cerebellar cases occurred in the first decade of life, or early in the second, while none of the hemispheral cases occurred in the first decade and only one in the second."

Bucy and Gustafson reported a series of 25 cases of cerebellar astrocytoma. In 5 cases the lesions were located strictly in the midline. The ages ranged from 3 to 14 years, with an average of 8.6 years. In 9 cases the tumor or its cyst involved the midline and one or both hemispheres. The patients' ages ranged from 22 months to 21 years. In the other 11 cases the lesion was confined to one of the hemispheres, and the ages ranged from 4 to 22 years, with an average of 10 years.

In 16 of the series presented here, according to the findings at operation or autopsy, the lesion was in the midline. The ages ranged from 5 weeks to 24 years, with an average of 10.3 years. In addition, in 11 cases the tumor or its cyst involved the midline and one or both hemispheres. The age in this group ranged from 2 to 39 years, with an average of 15.4 years. In 28 cases the tumor was limited to one hemisphere. The youngest patient in this group was 3 and the oldest 39 years of age, the average age being 18 years. Eight patients of this group were in their first decade of life. While, on the basis of these figures, no definite age differentiation can be made, there does not seem to be any distinctly greater tendency toward involvement of the midline in children and of the hemisphere in adults.

Diagnosis.—In the vast majority of the cases in this series there were symptoms and signs of progressively increasing intracranial pressure, as evidenced by headache of occipital or frontal localization, vomiting and failing vision. This syndrome of intracranial hypertension was sooner or later followed by subjective or objective evidence of cerebellar dysfunction. At the time of admission to the service, almost all the patients who proved to have strictly hemispheral location of the lesion showed the clinical syndrome of cerebellar involvement. However, only slightly above 50 per cent of the patients with midline or midline and hemispheral lesions gave evidence of the cerebellar syndrome.

In 2 instances the presence of signs of unilateral involvement of the pyramidal tract, along with the syndrome of increased intracranial pressure and slight cere-

bellar dysfunction, raised the problem of differentiation from tumors of the frontal lobe. Confirmatory evidence of a cerebellar lesion was obtained from preliminary air studies. In both cases the tumor, cystic in nature, was located in the right cerebellar hemisphere.

The question of differential diagnosis of a midline lesion in the middle fossa and one in the posterior fossa arose in 2 cases. In 1 of them, that of a girl aged 15, there was pronounced endocrine dysfunction, such as obesity, hirsutism and amenorrhea, together with signs of increased intracranial pressure. In the second case, there was primary optic nerve atrophy with temporal field defects, and roentgenograms showed enlargement of the sella turcica. In both cases ventriculographic studies indicated that the lesion was located in the posterior fossa, and at operation midline lesions were found.

In the 2 infants in this series, no tumor of the posterior fossa could be suspected. In 1 of them, with congenital occipital meningocele, the tumor was found accidentally post mortem. In the other, with congenital hydrocephalus, which proved to be obstructive in nature, exploration was made, and the tissue removed for biopsy resembled an astrocytoma.

Sex and Age Incidence.—In Cushing's series, the 76 cases were almost equally divided between the sexes. In Bergstrand's series of 56 patients from Olivecrona's clinic, 24 were females and 32 males. In the present series, 22 were females and 39 males.

The ages in Cushing's series ranged from 22 months to 41 years. The youngest patient among the 14 of the series of Elvidge, Penfield and Cone was 6 years of age; the oldest, 58. In Bucy and Gustafson's series of 25 cases, the ages ranged from 21 months to 22 years. In the present series, 2 patients were newborn infants, admitted to the service at the age of 5 and 6 weeks; the oldest patient was 39 years of age. The 2 infants are the youngest patients on record, and the cases will be described in more detail elsewhere.

Forty-three of the 64 cases in the present series, or 75 per cent, occurred in the first and second decades of life, and 18 were equally divided between the third and the fourth decade. This age distribution is approximately that found by Cushing, Bergstrand and others.

Duration of Symptoms.—The average preoperative duration of symptoms was 10.8 months, the shortest being one month and the longest sixty-five months. When the cases are distributed according to the location of the lesion, an interesting difference in preoperative duration of symptoms appear: The average duration for cases of strictly hemispheral location was 7.3 months, and the duration for cases of midline or midline and hemispheral involvement was 14.8 months.

Air Studies.—In one third of the cases, preliminary air studies were carried out. In the majority the picture obtained was one of symmetric dilatation of both lateral and third ventricles and of the anterior part of the sylvian aqueduct. In a few instances, in which the entire aqueduct and the fourth ventricle could be visualized, displacement of the iter or encroachment on the fourth ventricle enabled lateral localization of the tumor as well. In general, ventriculography was of great diagnostic aid in clinically obscure cases. On the other hand, it led to erroneous preoperative diagnoses in 2 cases, with fatal termination in 1.

In the latter, a man aged 31 had symptoms of dizziness on raising the head from the horizontal to the vertical position, with headache and tremor of the left arm. Examination showed choking of the disks, of 4 D, intention tremor of the left arm and dysdiadokokinesis on the left side. Air studies revealed a defect, in filling, involving the midportion of the right lateral ventricle, the anterior part of which was enlarged; the third ventricle, iter and fourth ventricle were normal;

exploration of the right frontotemporoparietal region revealed nothing abnormal. Autopsy revealed a cystic astrocytoma of the left cerebellar hemisphere.

In the second case, that of a 17 year old girl, there was a history of headache and vomiting for eighteen months prior to the patient's admission to the hospital, in October 1936. Papilledema and slight cerebellar signs on the right were found on examination. A combined ventriculogram and pneumoencephalogram showed encroachment on the posterior portion of the third ventricle. The roentgenologic diagnosis was pineal tumor. Craniotomy in the right occipitoparietal area and exploration through the corpus callosum revealed normal conditions in the region of the pineal gland. A second air study, two months later, indicated a lesion of the posterior fossa. Exploration revealed a semicystic tumor lying above the right cerebellar hemisphere and extending inward to the incisura of the tentorium.

These two cases show how easily an incorrect diagnosis can be made, owing to incomplete filling of the ventricles, which often occurs with lesions of the posterior fossa. In similar cases, in which the ventriculogram does not correspond to the clinical findings, a repetition of the air study is desirable.

Pathologic Picture.—Twelve tumors in this series were solid; all the others were cystic. Seven of the solid tumors were in the midline, and 5 were limited to a single hemisphere. In 2 cases, a second operation one year after the first revealed a cyst which had not previously been present. In a third case the tumor was found to be solid on two occasions, and only the third operation, seven years after the first, revealed a large cyst. In the large majority of cases of cystic astrocytoma the cyst was extraneoplastic, with the tumor as a part of the cyst wall. In a single case the cyst, containing 20 cc. of xanthochromic fluid, was intraneoplastic, the wall consisting entirely of tumor tissue. The solid portions of the cystic tumors varied in size from a nubbin, 1 cm. in diameter, to a mass 7 by 7 by 8 cm. Small cysts within the solid part of the tumor were common.

Microscopically, the tumors were composed of fibrillary and protoplasmic astrocytes. In many instances, both types of cells were observed in the same tumor, the proportion differing from one area to another. According to Bailey, the tumors could be classified as fibrillary, predominantly fibrillary or protoplasmic astrocytomas. The fibrillary astrocytomas varied greatly as to the number of fibrils, some being composed of many fibrils and few cells and others of many cells and only a few fibrils. Vascularization in most instances was poor; in only 2 tumors was pronounced proliferation of vessels observed, giving the tumor an angiomatous appearance. Hyalinization and areas of calcification were occasionally seen.

In 2 cases seeding was suggested symptomatically by slowly developing paraplegia. However, it could not be proved, even in a case in which laminectomy was carried out.

Origin of the Tumor.—Cushing, in his review of cerebellar astrocytomas, stated: "The tumors are probably of congenital origin and usually date symptomatically from childhood." Bergstrand expressed the belief that the astrocytomas are malformations—not tumors. Bucy and Gustafson, in discussing Bergstrand's view, disproved it and stated repeatedly that the cerebellar astrocytomas may be congenital tumors or arise from a developmental fault but that there is no proof for such a hypothesis. The following 2 cases in our series may throw light on the origin of the cerebellar astrocytomas.

CASE 1.—A 5 week old infant was admitted to the hospital on June 26, 1932, with an occipital meningocele, which had been present since birth. Physical and neurologic examination revealed nothing abnormal. Roentgenograms of the skull showed delay in calcification of the cranial bones, with a defect in the occipital region. The meningocele was excised and the defect repaired. The infant died several hours after the operation.

The brain, examined post mortem by Dr. B. J. Alpers, showed grossly almost total absence of the cerebellum and a greatly thickened pia-arachnoid membrane over the entire base of the brain. Except for a part of the inferior portion of the vermis, the paraflocculi and some of the superior portion of the vermis, no cerebellar structure could be found. The cerebellar hemispheres were entirely absent. Beginning in the posterior portion of the midbrain and involving the inferior colliculi was a tumor. This extended into the tegmentum of the pons, filling the fourth ventricle. As the tumor extended backward, it seemed to become part of the cerebellum. The aqueduct and the fourth ventricle were plugged with this abnormal tissue. The lateral and third ventricles were greatly dilated.

Microscopically, the tumor appeared to rise from the region of the colliculus and to be attached to this area by a small peduncle. This was covered with ependyma for a short distance, but this lining was soon lost over the surface of the tumor. In the area of transition the collicular tissue was rarefied, showing loss of ganglion cells. The pedunculated portion of the tumor, which was lined with ependyma in several layers, consisted of ganglion and glia cells, lying in a fairly well preserved matrix of nerve tissue and passing rather abruptly into tumor tissue. Tongues of nerve tissue, however, extended from this area into the tumor. These peninsulas of nerve tissue appeared as septums within the tumor. The latter was quite cellular and not very vascular. The cells were of uniform type, arranged in no definite fashion. These cells had a small, round nucleus, with a well defined membrane and clumps of chromatin arranged around the membrane. The cells lay in a fibrillar matrix, which was glial by nature.

Case 2.—A 6 week old infant was admitted to the hospital on Jan. 14, 1936. The child had been delivered by forceps and showed normal development. A large head was noticed at birth, and the size had been increasing rapidly since.

Examination revealed that the circumference of the head was 18 inches (45.72 cm.), the forehead high and frontal bosses prominent. Fontanels were huge, and ossification was retarded. A subdural puncture, performed bilaterally, revealed clear xanthochromic fluid, 45 cc. of which was removed from each side. A combined ventriculogram and encephalogram showed that the whole ventricular system was greatly dilated. There was a distinct filling defect between the fourth ventricle and the dilated aqueduct. Apparently, the air shown in the aqueduct was part of that introduced into the ventricle, while that in the fourth ventricle was air introduced by the lumbar route.

At the exploration on March 9, a false membrane occluding the passage from the aqueduct to the fourth ventricle was found. Part of it was taken for histologic examination. The infant died soon after this procedure. Permission for autopsy could not be obtained. The histologic picture of the tissue removed was that of a fibrillary astrocytoma.

Comment on Cases 1 and 2: In the first case, an abnormal mass of tissue was no doubt present at birth. This was combined with almost complete agenesis of the cerebellum and an occipital meningocele. This anomaly and the presence of septums of nerve tissue within the tumor suggest that the mass arose from a developmental fault. In the second case, the data are not complete. The only evidence was the presence of abnormal tissue in the form of a membrane occluding the outlet of the aqueduct. The hydrocephalus, present at birth, showed that this defect was congenital. In both cases, abnormal masses of tissue were present which bore a histologic resemblance to astrocytomas. These astrocytomatous tissue masses support the hypothesis that the tumor was congenital.

Results.—One of our patients died before surgical intervention. Among the 60 remaining patients, there were 17 postoperative fatalities from first or successive

operations, a surgical case mortality of 32 per cent. However, among the 27 patients operated on since January 1937 (when the head of the service changed), only 4 died. In 1 of the latter exploration was carried out for the third time, over eight years after the first operation. It is clear, then, that with the acquisition of more knowledge regarding the surgical treatment of this type of tumor and the establishment of a consistent plan of action, the mortality rate can be notably reduced. This is indicated by the most recent consecutive 25 cases, in which there were no operative fatalities.

Five patients died suddenly one-half to four and one-half years after the operation, and outside the hospital. Six others cannot be traced at the time of this report but were followed for periods of three to twenty years. The remaining 25 patients are still living, 8 having survived ten or more years.

DISCUSSION

Dr. Leo Davidoff, New York: My experience with the cerebellar astrocytomas consists of a series of 40 cases. I have little to add to what Dr. Grant has said about the clinical picture presented by these tumors. I have not been able to distinguish tumors of the vermis from those of the hemisphere on the basis of statistics, showing that the tumors of the vermis, or the midline tumors, occur in the younger age group, although this certainly appears to be the tendency from Dr. Grant's figures. The only clinical point I wish to make is one already observed by Dr. Cushing, namely, that the children harboring these tumors are unusually bright, unusually lovable, unusually cooperative: the kind of children that the interns referred to as "angel" children, without any preconceived notion as to the prognosis from the operation.

Dr. Loretta Bender has come on the same idea from a study of children with cerebellar lesions, whether tumors or otherwise, and her psychologic explanation is that the children are unsteady on their feet and so tend to cling to the adult for support and are amenable for that reason. Whether that is the explanation or not, it is, nevertheless, a clinical observation.

As for the diagnosis, I would make just one point, and that is with regard to the roentgenogram. Dr. Grant cites 2 cases in which the ventriculogram misled him; that can happen, but I have found that if one makes ventriculographic studies, with at least one midline ventriculogram, one will frequently see the fourth ventricle and the distorted aqueduct, which may not be visible in the ordinary, even the stereoscopic, view. We find it worth while, therefore, to make such ventriculograms in these cases.

The surgical results conform, too, to what Dr. Grant has shown; perhaps I can show briefly, in a few slides, the results which my colleagues and I have had in our series.

I think that what Dr. Grant has emphasized is very important, namely, that these tumors must be removed from the obstructive position which they hold. Thus, for example, in 15 cases in which the tumor was completely removed in our series, there was no operative mortality and the survival period was as long as seventeen years.

In the case of incomplete removal, the patient, even if he survives the operation, comes back for later operations, and it is with the second, third or fourth operation that the mortality occurs.

The next slide shows 3 cases in which apparently a decompression was done without a verification of the tumor and the decompression served to tide the patients over for one, two and three years, respectively. Eventually, reoperations were performed, and 2 of the patients died.

The next slide shows 2 cases in which the cyst was evacuated initially. In both cases a second operation was done, one, two or three years later. In 1 case the tumor was removed and the cyst evacuated, and in 1 a total removal of the tumor was performed, at the second operation. In both cases the cysts were again reopened, one and four years later, and total removal was accomplished. Both patients are well now, eleven and thirteen years later.

The next slide shows the over-all results: Twenty-five of the 40 patients are now known to be well, with total removal of the tumor in 17. The operative mortality on the initial operation was only 7.5 per cent; but on the second operation it was 17 per cent; on the third operation 3 of 6 patients died, and the patient who had a fourth operation died. The total operative mortality, 9 of 59 patients, was similar to Dr. Grant's figures.

These figures show, then, that the primary object should be to remove the tumor *in toto* at the first operation. That offers the best chance for survival. If, for any reason, that cannot be done, and operation has to be done later, one must count on a higher operative mortality.

We have found that in some of these cases postoperative radiation therapy is valuable, and I have even gone so far as to give radiation therapy in those cases in which I felt at the operating table that I had removed the whole tumor. This precaution is based on several cases in which recurrences took place when I thought the tumor was completely removed. However, there is a great difference of opinion as to the value of radiation therapy.

This must be said: The cerebellar astrocytoma when removed *in toto* from a child, or an adult for that matter, is the most benign in all neurosurgical experience. The patient recovers without any sequelae and is completely well, and he does not suffer from the residua of so many patients with cerebral tumors, even if benign, like a meningioma.

Dr. Eli Jefferson Browder, Brooklyn: I find myself in entire agreement with the excellent presentation of Dr. Grant and with Dr. Davidoff's comments. I should like to extend the statistics a bit and point out that, given a child with a cerebral tumor, regardless of the position, there is about a 25 per cent chance that that child has an astrocytoma. In my own series of 142 tumors in children, 31 were astrocytomas and 32 were medulloblastomas. I wonder whether one can ever be sure that one has totally removed this tumor. The cerebellar astrocytoma is a very chronic lesion and no doubt persists for years without unusual symptoms. For example, in 1932, an 8 year old girl with obvious evidence of tumor of the posterior fossa had an exploration, and an astrocytoma was disclosed. It was subtotally removed, since a portion of the mass was attached to the brain stem. At present, sixteen years later, she is perfectly well, has married and has had one child. If this tumor had been "totally removed," we should have felt very sure that it was totally extirpated in the light of a survival period of sixteen years.

Dr. Stevenson has pointed out clearly, in 1 instance in particular, the great chronicity of these tumors. I do not mean to imply that one should not attempt total removal. However, I think many of the cures following surgical treatment may be attributed partly to the slow growth of these neoplasms.

Dr. Francis C. Grant, Philadelphia: I want to thank Dr. Davidoff and Dr. Browder for discussing this paper. I know from experience the amount of trouble to which Dr. Davidoff must have been put to get together his strikingly successful series of figures.

I agree entirely with Dr. Browder about the possibility, in fact the probability, that some of these tumors are not totally removed. I had my training under Dr. Frazier. Dr. Frazier had a tremendous distaste for exploring the vermis and

the fourth ventricle. After I had seen Dr. Cushing split the vermis and expose these tumors, it seemed quite possible that complete removal could, at least, be attempted. The tumors of the cerebellar hemisphere present, of course, an entirely different problem from those that involve the vermis.

These astrocytomas are distinctly benign. If such a tumor is found in the vermis, involving the midline, and one is convinced, either by the appearance of the tumor or by quick staining methods, that it is an astrocytoma, every effort should be exerted to extirpate the tumor completely, no matter how high it extends. The important point is to be certain that the aqueduct is unblocked. If block of the aqueduct is relieved, the mortality will be tremendously reduced, since circulation of the cerebrospinal fluid is restored. Incidentally, the morbidity rate and the postoperative period of survival of the patient will be increased.

These tumors are benign, and therefore, as Dr. Davidoff has stated, they should be vigorously attacked the first time that they are encountered. The results of secondary operative procedures are never as satisfactory as an attempted radical removal at the first surgical session.

Thalamotomy in Mental Disorders. Drs. E. A. Spiegel, H. T. Wycis and H. Freed, Philadelphia.

This new operative procedure for mental disorders attempts to obtain the beneficial effects of prefrontal lobotomy, particularly in the emotional sphere, and to avoid its undesirable side effects as far as posible. In prefrontal lobotomy one cuts through the white matter of the frontal lobe, interrupting the connections of the frontal association areas with other parts of the cerebral cortex and with subcortical ganglia; often one also produces unintended lesions, particularly of the basal ganglia. Thalamotomy produces small circumscribed lesions in the dorsomedial nucleus of the thalamus, the nucleus which degenerates after prefrontal lobotomy (Freeman and Watts and others); one attempts in this way to interfere with the corticothalamic interrelationships underlying emotions. The lesions are produced by means of the so-called stereotaxic technic, which has so far been used in animal experimentation only (Horsley and Clarke), and which we have adapted for use on the human brain. The patients were selected according to indications similar to those for prefrontal lobotomy. Most of the patients had been inmates of institutions for two to eight years and had been subjected to various types of psychotherapy and shock treatment without relief. For 1 patient only, with catatonic schizophrenia, the duration of the disease was relatively short (four months). In preliminary work on animals and human cadavers, we learned to regulate the strength and duration of the current so that lesions 3 mm. in diameter resulted, covering about one thirty-sixth of the volume of the dorsomedial nucleus. One to two such lesions placed in each dorsomedial nucleus had no, or only a transitory, effect (3 patients). In 8 patients five such lesions were produced in each dorsomedial nucleus.

Similarly, as after prefrontal lobotomy, in the first stage following thalamotomy the patient exhibited somnolence, disorientation (chiefly for time), memory defects, inertia and, then, psychomotor retardation. Two patients had transitory weakness of one leg (maximum duration, twenty days), associated with a Babinski sign and/or ankle clonus. Gross sensory disturbances or impairment of the so-called psychoreflexes was not demonstrable. In the vegetative sphere, there was frequently increased appetite, leading to increase in weight. In 1 patient with hypertension the blood pressure fell temporarily from an average of 190 systolic and 110 diastolic to one of 130 systolic and 95 diastolic. In 4 patients transitory vesical incontinence developed (lasting from a few days up to three weeks).

A favorable effect on pathologic symptoms was obtained, particularly in nervous tension, anxiety, depression, irritability, agitation, hallucinations and compulsions. Rorschach studies, carried out by Mrs. C. Krusen Scholz, pointed in a similar direction.

Except for 1 patient, whose preoperative low intelligent quotient (77) dropped to 67, no impairment of intelligence was demonstrable in tests (performed by Mrs. F. Nasife and Miss P. C. Walsh), although the speed of response was slowed similarly, as in Hunt's observations after prefrontal lobotomy. In some cases there was even a certain improvement in the score. One of the 11 patients died, apparently as a result of an attempt to change the type of electrode; of the 8 patients with five lesions on each side, 3 are still institutionalized and 4 returned home; 1 of these is now trying to find employment. With regard to long-lasting side effects of the operation, 1 patient had impairment of memory, and 4 patients, some diminution of initiative; 1 of these had been subjected to prefrontal lobotomy at another institution two years prior to the thalamotomy, so that this condition was probably the combined effect of these two procedures. The latter patient is also careless in personal appearance. Up to the present time there has not developed in any of our patients such annoying sequelae of prefrontal lobotomy as distractibility, childishness, undue facetiousness or lack of tact or of discipline. One of the most disturbing sequelae of prefrontal lobotomy, epileptiform convulsions, did not appear in our material. Electroencephalograms showed no changes, or only slight transitory slowing, particularly in the frontal leads.

Our main goal in this first part of our work was to ascertain the minimal lesions which could produce a therapeutic effect. We were, therefore, satisfied with five lesions covering about one seventh of the volume of the dorsomedial nucleus. Only in 1 case was the operation performed three times so that our maximum lesion covered still less than one-half the volume of the dorsomedial nucleus. Our material is, of course, much too small to permit any statistical conclusions, and this communication is of a preliminary nature only. These studies are being continued, since experiences in a greater number of cases and for long periods are required in order that this method may properly be evaluated. Our experiences, however, may permit at least one conclusion. They show that lesions limited to the dorsomedial nucleus of the thalamus can relieve anxiety, emotional tension and allied symptoms in patients with psychoses and obsessive-compulsive states.

DISCUSSION

DR. J. L. POOL, New York: I consider this contribution a great advance in the knowledge and concept of the surgical treatment of the psychoses.

Ever since the introduction of prefrontal lobotomy, continued efforts have been made to determine more precisely what pathways or structures of the brain must be interfered with in order that beneficial results may be achieved without the unfortunate effects that sometimes follow lobotomy and allied procedures.

Thus, Freeman and Watts tested the effects of various quadrantic sections of the prefrontal matter, and others, such as Hofstatter and associates, have done likewise.

In another approach to the problem, limited cortical ablations have been tried (Penfield, Pool, Heath and others). From these data, it is my tentative impression that the removal of cortex from the region of Brodmann areas 9 and 10 bilaterally is at present the most effective procedure carried out on the cortex of the brain, involving the maximal benefit and the least detriment to a psychotic patient requiring surgical treatment. This impression, deriving largely from studies of patients on whom topectomy has been performed, is another link in the chain of evidence suggesting that the important circuit, interruptions of which may lead to improvement in certain psychotic states, involves the rostromedial portion of the

prefrontal cortex (areas 9 and 10), the underlying white matter and the dorsomedial nuclei of the thalamus, as pointed out in Dr. Spiegel's paper.

Recent experimental work by Ward and McCullough, moreover, has revealed projections between the prefrontal cortex and the hypothalamus, suggesting that the nuclei of the hypothalamus may play an important part in the circuit just mentioned.

I should like to mention the possibility of a direct surgical approach to the thalamus. Stimulated by Dr. Spiegel's paper, I recently exposed the thalamus easily by making an incision through the corpus callosum into the lateral ventricle.

In conclusion, I may say that this paper is of great value. Not only is it stimulating, but it supplies direct knowledge of a link often speculated on by neurologists, and it opens up a vast vista for future work on corticothalamichypothalamic circuits.

Dr. Lothar B. Kalinowsky, New York: Those of us who are laboring with the problems involved in psychosurgery can only be deeply impressed by this presentation. It could be expected that thinking in terms of brain physiology would lead sooner or later to the idea of shifting the field of action from the widely extending projection fibers of the white matter and from the cortex to the dorsomedial nucleus of the thalamus, where the pathways which are to be interrupted converge. A. Meyer and his co-workers found that patch degenerations of widely varying degree in the dorsomedial nucleus were sufficient for excellent clinical results. It is not necessary to destroy the entire dorsomedial nucleus. Apparently, also, it does not greatly matter which parts of the nucleus are made to degenerate, and it may be hoped that the lack of precision for which the Horsley-Clarke instrument was blamed by some neurophysiologists is actually not an important factor militating against the efficacy of the operation. If the view is correct that indications for destruction of the lower part of the fronal lobe differ from those for destruction of the upper part, selective thalamotomies should be possible, in view of Walker's findings that the medial part of the dorsomedial nucleus projects to the orbital area of the cortex and the lateral part of the convexity.

Although psychometric tests even after extensive lobotomy reveal no impairment of intellectual performance, interviews with the patient or with his relatives do show it. This explains the increasing number of attempts at less extensive operations, such as partial lobotomies, including the transorbital operation, which actually is a partial lobotomy, and the cortical operations of gyrectomy and topectomy. Thalamotomy should give the least side effects, for two reasons: A wire placed by the Horsley-Clarke technic should destroy only a minimal amount of cortical tissue and white matter, and the operation can be carried out in varying degrees at several stages. The minimal amount of cortical damage should, furthermore, decrease the danger of postoperative epilepsy. The theoretic interest of thalamotomy for the basic concepts in psychiatry is another reason that we are greatly indebted to the authors for this presentation.

Dr. Walter Freeman, Washington, D. C.: I have investigated the thalamus after prefrontal lobotomy in probably a dozen cases, and, by correlating the findings with the incisions in the various portions and planes, have been able to map out the topography of the thalamic projection to a certain extent. Essentially, one might say that the medial, or paraventricular, portion of the medial nucleus projects to the base of the frontal lobe. The central part of the nucleus projects to the frontal pole, and the lateral part, to the convexity. With that orientation, which is fairly well established, the work of Spiegel, Wycis and Freed finds a thorough justification.

I am very glad that Watts and I, in our paper on the thalamus, suggested that since the cortex was intact after thalamotomy the essential lesion of the thalamus might well be the cause of the improvement in the emotional condition of these

patients. That theory, and it was only a theory, has found abundant justification in the work of the authors. I want to congratulate them and to say that next month I am going to say something about the undercutting of areas 9 and 10.

Dr. Herbert Freed, Philadelphia: A few interesting observations on the Rorschach test might be worth noting at this time. For 6 patients we evaluated the Rorschach responses before and after operation. We found a diminution of responses indicating anxiety. They exhibited greater freedom in showing instinctive drives, while maintaining ego controls and a tendency toward better contact with reality. Four of the 6 patients showed evidence of an organic lesion of the brain according to the usual Rorschach criteria. This was manifested by slowing of reaction times and a tendency toward perseveration.

We are not drawing any final conclusion from these studies, for we wish to study first the control patients on whom preliminary procedures have been carried out, and we wish to make further studies on the 6 patients.

Dr. Ernest Spiegel, Philadelphia: I am greatly interested in the work on topectomy of the Columbia group. A comparison of the effects of thalamotomy and topectomy should be of great value, for thalamotomy involves the subcortical component, whereas in topectomy one is concerned with the origin of fibers connecting the frontal lobe and the thalamus, on the one hand, and the origin of association systems, on the other.

Another question Dr. Pool has raised concerned the relation of the thalamus to the hypothalamus. Anatomically, it is known that the periventricular area contains fibers connecting the hypothalamus and the medial nucleus.

Several years ago, with Dr. H. Miller of New York, we carried out experiments in which we studied the effect of lesions of these systems somewhat below the thalamus, in the so-called subthalamus. In this group of experiments we found that we were able to produce a transitory state of somnolence and catalepsy in cats, with the hypothalamus histologically intact. At that time we were inclined to assume—but had no definite proof—that this disturbance was due to interference with the relation of thalamic areas to the hypothalamus. The subsequent work here mentioned may substantiate the existence of such relationships. After thalamotomy we found changes in the vegetative functions, as was mentioned, and it is quite possible—and this is a question we have not analyzed as yet—that these vegetative disturbances may be partly the effect of direct lesions of the nucleus medialis and partly the effect of lesions of fiber systems connecting the hypothalamus and the nucleus medialis, or of frontohypothalamic connections.

Dr. Kalinowsky has mentioned patch degeneration of the dorsomedial nucleus. The work of Dr. Freeman points in a similar direction. That encouraged me to believe that small lesions in the medial nucleus might be sufficient, and we tried to produce a type of patchy lesion only at five points—they are certainly not large lesions—and leave a part of the nucleus intact. Whether it will be advisable to change the location of these lesions, or whether five are sufficient, only the future will show.

The work of Dr. Freeman was a great support for our studies, because it gave an anatomic foundation for our assumption that the impairment of the dorsomedial nucleus is largely responsible for the beneficial effect of these operations.

The accuracy of stereotactically produced lesions depends on the careful application of the apparatus for operation in exactly the same position as in the preoperative roentgenologic study from which the coordinates of the lesion are computed. After producing the lesion, we injected a droplet of ethyl iodophenylundecylate (pantopaque®) into the destroyed area; postoperative roentgenologic studies showed what a high degree of accuracy in placing the lesions can be attained.

NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY, AND THE NEW YORK NEUROLOGICAL SOCIETY

Robert B. McGraw, M.D., *Chairman, Section of Neurology and Psychiatry, Presiding*

Combined Meeting, Feb. 8, 1949

Psychosomatic Aspects of Genuine Epilepsy. DR. ALFRED SCHICK (by invitation).

The electroencephalographic and statistical investigation of blood relatives of epileptic patients has suggested the presence of an innate predisposition to the seizures. The constitutional potentiality toward compulsive disorders may occur with a greater potentiality toward the development of neurotic disturbances. The brain imperfection of epilepsy may be a pathogenic agent which interferes with the normal individual development and personality integration. This assumption may throw light on the significance of the psychologic component in the pathologic basis of some seizures.

From the analysis of 4 cases, 1 of which was reported in detail, it was concluded that a number of persons with the epileptic syndrome are under the pressure of pent-up emotions. This condition may influence the vegetative apparatus and may produce an exaggerated emotional response to stimuli. It is suggested that in such persons any increase of affective tension, in which the ubiquitous anxiety seems to be of major importance, may cause temporary homeostatic changes in the brain which are likely to initiate an attack.

The motor, sensory and intellectual phenomena characterizing the aura are remnants and reminiscences of mental events of which the patient has never become fully aware. They are decipherable, like the fragments of a dream, and may give a clue to the motives and psychodynamics of the seizure. The latter may be compared psychosomatically with an organ neurotic symptom in the sense that an emotion touches off a physiopsychologic mechanism. It may resemble that type of organ neurotic symptom classified as an affect equivalent. It might be employed for instinctual release and secondarily become a conversion symptom. Thus, it may represent for the patient a partial realization of his unconscious aspirations, the specific emotional charge of which has been contributing to the onset of the seizures.

Physiologic Aspects of Epilepsy. DR. H. HOUSTON MERRITT.

Seizures occur spontaneously or may be artificially produced in practically all animals. It may be concluded, therefore, that seizures are a manifestation of the reaction of an organism to a disturbance in the internal milieu. It is self evident that external stimuli can produce a reaction only by alteration of the internal milieu. In some persons the disturbance which produces a seizure must be of catastrophic proportions, for example, electric shock, metrazol® shock or severe cerebral anoxia. In others the internal equilibrium is in such delicate balance that an attack can be precipitated by a minor physiologic disturbance, such as that produced by hyperventilation.

Studies of the electric potentials of the cerebral cortex have shown that in persons who are subject to frequent seizures there is a constant or frequent paroxysmal burst of abnormal cortical activity in the interim between seizures and that at the onset of an attack this abnormal activity is increased. The abnormal activity may burst forth suddenly in all areas of the cortex, or it may start in an isolated focus and spread rapidy to other portions of the brain.

The nature of the disturbance of the internal milieu which alters the activity of the cortical neurons and precipitates a seizure is as yet unknown. In fact, there is no evidence to conclude that the final metabolic derangement which results in a

seizure is the same in all patients or the same at different times in any one patient. For many years it was considered possible that oxygen deprivation was the common factor which caused the cortical neurons to discharge in an explosive manner and precipitate a convulsion. In recent years, however, evidence is accumulating which suggests that a disturbance in one of the enzyme systems, possibly that which regulates the action of acetylcholine, is the common factor.

In addition to agents which directly alter the internal milieu, seizures in susceptible persons may be precipitated by factors in the external environment. Although external precipitation of convulsions is relatively rare, seizures may occasionally be produced by such external stimuli as sound, visual stimuli, cutaneous stimuli and acute emotional experiences. An interesting experiment of Gibbs throws light on the mechanism of the production of seizures by external stimuli. Gibbs confirmed previous observations that there is often an increase in the degree of abnormality in the electroencephalograms of most patients during sleep. Indeed, in some cases in which waking records were normal, focal or generalized abnormalities appeared in the sleep record. Most significant, however, was the observation that if a sudden stimulus was given at the moment when there was an excessive degree of abnormality in the electroencephalogram a seizure could be precipitated in some cases.

In summary, it can be stated that a seizure is the result of a disturbance in the internal milieu regulating the activity of the cortical cells. In persons with a stable internal milieu the stimulus which produces a seizure will have to be great. In others, the so-called epileptic persons, in whom the equilibrium is in an unstable state, seizures may occur much more readily. The disturbance which produces the seizures is usually independent of external stimuli and will be precipitated by the latter only when the balance is especially precarious.

DISCUSSION ON PAPERS BY DRS. SCHICK AND MERRITT

Dr. Paul H. Hoch (by invitation): We all agree that epilepsy is an organic disorder and that in epileptic persons the tendency to periodic discharges may be demonstrated clinically and electroencephalographically. Dr. Merritt has pointed out that these discharges can be precipitated by many factors, for instance, chemical, toxic and mechanical influences. Attention is being focused increasingly on those discharges which are precipitated by emotional events and in which some psychogenic mechanism is involved. I believe that the discharge based on emotional events has as much an organic basis as that which is precipitated by a chemical, physical or mechanical factor. It is not yet known how the metabolic part is mediated; anxiety, tension, etc., produce a profound effect on the metabolism of the brain, and it is obvious that they have a very large influence on epileptic discharges. The question is not whether the emotional factor serves as a trigger to set off seizures, but how often this takes place and in how many epileptic persons. Dr. Merritt has just pointed out that a few isolated cases are not enough to prove that this is a universal mechanism in epilepsy; reliable statistics are needed to know how often and in what kind of epilepsy the mechanism operates.

Dr. Schick, in a well worked-out paper, described how libidinal disturbances are able to produce epileptic manifestations. Libidinal disturbances in epilepsy are interesting. If you examine a number of patients, and especially if you treat them psychoanalytically, it is obvious that a great many show oral, anal and passive or aggressive tendencies, and psychosexual infantilism in many of the patients is apparent. In many, as Dr. Schick has demonstrated in his paper, oedipal conflicts are also present. However, all these mechanisms which Dr. Schick traced in his patients, and which have been described by a number of others, are not specific to

epilepsy. In all kinds of neuroses, and even in some psychoses, similar dynamics can be demonstrated, and therefore a specific mechanism is still unproved. For instance, in a number of schizophrenic patients the same libidinal regression can be demonstrated. This is an interesting phenomenologic relationship. Only one specific dynamic factor emerged in epilepsy, and that was the frequency of rebirth fantasies which these patients experienced in relation to catastrophic anxiety connected with the seizures.

In an analysis of the mechanisms in epilepsy, three questions emerge: 1. Are the psychodynamic factors produced by epilepsy an organic process *per se*? 2. Are they reactions of the patient to the awareness that he has epilepsy? This is a distressing handicap socially. 3. In how many persons are a neurosis and epilepsy coincidental, with the two conditions influencing each other? Neurosis is a very common disease, and epilepsy is fairly frequent. It is obvious, therefore, that the two will occur in some persons, especially when environmental factors play a role in producing emotional tensions.

Dr. Schick made two interesting suggestions, namely (1) that in epilepsy secondary conversion mechanisms are frequently used and (2) that, in his opinion, epilepsy resembles an organ neurosis. I do not believe that we shall quarrel with the first statement, that secondary conversion mechanisms in epilepsy are fairly common. Bratz, who described hysteroepilepsy, pointed out that a great many epileptic patients used a secondary conversion mechanism which imitated the original organic disorder. This is not surprising, for one sees it in other organic disorders or in persons with organic inferiorities, as Adler noted long ago. Dr. Schick's second suggestion I cannot follow so readily, because an organ neurosis is something different from that which one observes in epilepsy. Hendrick's statement that discharge through the central nervous system is replaced by the discharge of autonomic tension is evidently incorrect, because discharge is present on both levels and no replacement takes place, and because autonomic discharge is as common as cerebral discharge and the two are usually linked. According to Fenichel's description, an organ neurosis is not present, because actually all the so-called neurotic manifestations can be obtained in these patients, in addition to the fits. Therefore the discharge is not absorbed by the somatic mechanism *per se*. Finally, it must be mentioned that in an organ neurosis it is assumed that the patient's somatic difficulty is caused, or to a large extent produced, by the constant tension and anxiety based on the psychodynamic situation in existence. We agree that in epilepsy an organic substratum is released or precipitated by a psychogenic factor, and therefore I believe the two should be kept distinct and that epilepsy should be considered a disorder in which an organic substratum is the basis. However, trigger mechanisms can act on it, and the emotional factor is one trigger of many. This is frankly recognized in the treatment of epileptic patients. They receive medical treatment for the organic condition and psychotherapy for the emotional trigger, and in many clinics where children are treated for epilepsy the child receives medication and the mother psychotherapy.

DR. CHARLES BRENNER (by invitation): Dr. Merritt made an essential point, namely, that the ability to react with a convulsive seizure in itself is a normal property of the cortex of any of the higher mammals. The questions of how a seizure is precipitated and what function, if any, it serves in the economy of the individual organism are matters which are much more obscure. We shall have to conclude that, so far as we know at present, the difference between patients who show convulsive seizures sporadically and those who are normally free from such seizures is a quantitative one, and is perhaps an expression of the ease with which this particular type of response is elicited from the cortex.

A question which seems to me of some importance is how to apply the various facts presented this evening to the problem of the treatment of the patient with convulsive seizures. Dr. Hoch pointed out in many clinics the effort is made to apply all the knowledge available, both from the psychologic and from the physiologic side, to the task of treatment, but often the physician is faced with the practical necessity of limiting his therapeutic efforts to those which are most likely to be effective. My own impression is that at the present, at any rate, much more is known about how to raise the threshold of the cortex against a convulsive seizure by the administration of various anticonvulsant drugs than about protecting the patient from seizures by any other method. Drug therapy is simple, and it is fairly effective with many patients, particularly those with grand mal and psychomotor seizures. There is no question that there are many patients for whom attention to their psychologic problems is essential for a good therapeutic result. However, I should say that the pharmacologic treatment of the seizures, that is, the application of our understanding of the physiologic elements in the genesis of epilepsy, is more important.

I should like to ask Dr. Merritt's opinion about the relative importance in the production of convulsive seizures of disorders of metabolism of the cortex and disorders of metabolism in lower centers of the brain. I should like to know Dr. Schick's opinion as to the frequency of such cases as the one he presented, in which it would appear that psychologic factors are really essential for the production of fits. I am also interested in knowing his opinion of the effectiveness of psychoanalytic or other psychotherapeutic procedures in such cases.

Dr. Wayne Barker (by invitation): These two excellent papers demonstrate the situation one faces in approaching the problem of epilepsy. On the one hand are the soundly supported facts of electrophysiology, and on the other is the equally well established evidence of psychopathology. Any one who studies a large number of convulsive patients and who is familiar with the various modes of approach to the understanding of personality and cerebral function in the neuropsychiatric disorders soon finds some justification for all points of view. Rather, I should say, the investigator will be presented with this varying evidence as the patient's story unfolds.

Dr. Schick's paper, which presents the psychoanalytic rather than the psychosomatic point of view—he states that the somatic aspects are in the province of the psychiatrist—presents material which may be secured from a number of patients. Hendrick (Hendrick, I.: *Psychosom. Med.* **2**: 43, 1940) and Masserman (Masserman, J.: *J. Nerv. & Ment. Dis.* **79**: 377, 1934) have published evidence that the warning phenomena preceding a fit seem to serve, in some cases, as a crystallized reenactment of some anxiety-laden experience of the past. Reich's view (Reich, W.: Die Funktion des Orgasmus, Vienna, International Psychol-Analytical Press, Verlag, 1927) of the convulsion as an extragenital orgasm is supported by those patients who describe their convulsive and their sexual experiences in almost exactly the same terms. Other psychoanalytic views find patients also to whom their particular formulation seems peculiarly apt.

Some patients behave as though their convulsive symptoms were produced by mechanisms operating with the intention of confirming the theories of Pavolv and his followers. Many patients do behave in the fashion described by Levin (Levin, M.: *J. Neurol. & Psychopath.* **16**: 256, 1936), that is, as though their brains were suddenly "crowded" with excitation or inhibition. Other persons with convulsions provide little evidence for any of these formulations but, rather, behave as though they might respond with a fit to any intense somatic or life situation stress and thus conform to psychobiologic views.

The "psychosomatic" point of view was expressed centuries ago by Galen (Galen, translated by O. Temkin, *Bull. Inst. Hist. Med.* **2**: 178, 1934) in his "Advice for an Epileptic Boy." Every clinician with any great experience with convulsive patients knows that symptoms may be more frequent in times of stress and less frequent in periods of tranquillity. The problem is not whether epilepsy is "organic" or "psychogenic"; the problem is what disturbances from within or without can so interfere with cerebral function as to bring about the convulsion situation. "The convulsion is but a symptom," as Hughlings Jackson never tired of saying, and, as Kinnier Wilson took pains to point out, "No such disease as epilepsy exists or can exist." The convulsion mechanism is present in the brains of all men. Apparently, some persons go through life without having this mechanism tripped even once. Others have fits with childhood febrile episodes or at extremely rare intervals, like Wilson's patient, who had her first convulsion at the age of 14, during the onset of her reproductive activity, and her second fit at 44, at its close.

Sparing further detail, it is clear that the problem is that of the cause of the individual fit. Since the advent of electroencephalography, it has been assumed that convulsions, and the abnormal brain waves with which they are associated, are produced by spontaneous "explosions" of the metabolic and electrical activity of brain cells. There has been a tendency on the part of those who work from this "organic" point of view to consider convulsive phenomena only from the point of the nerve cells involved; that is, this view deprives the convulsion of its afferent segment. On the other hand, one might say that the psychodynamic point of view tends to overemphasize the largely symbolic means of convulsive behavior and to ignore the neurophysiologic substrate on which these symbols are based.

In a series of patients studied at the New York Hospital and at a veterans administration hospital, my colleagues and I have observed that abnormalities of the brain wave pattern accompany certain nonconvulsive reactions of epileptic patients during experimental interviews (Barker, W.; Burgwin, S., and Simons, D. J.: *J. Nerv. & Ment. Dis.*, to be published). These reactions occur as disruptions of the stream of talk and behavior as associated with the patient's discussion of significant aspects of his life situation which seem to have a bearing on his convulsive illness. The patient reacts as though he were suddenly brought to a standstill or an impassé in his consideration of his problems. It may be that the sudden development or realization of an irreconcilable conflict or a defense against painful awareness if he proceeds further brings the patient to a standstill. In any case, there is a hesitation or cessation reaction, which may be accompanied with signs of tension, such as swallowing, adventitious movement or sighing, and followed by changing of the subject or other defensive operation. Various forms of abnormal waves have been observed to accompany the standstill reaction.

This fact may provide a basis for bringing together the so-called psychogenic and organic points of view into a unitary psychosomatic concept of convulsive behavior. Two other facts must be cited to clarify this point. First, there is a biologic reaction called the "still reaction," about which Byrne (Byrne, J. G.: Studies on the Physiology of the Eye, Still Reaction, etc., London, H. K. Lewis & Co., Ltd., 1942) has written extensively. This reaction is observed in all animal forms to occur in response to alerting stimuli as a prelude to behavior comprised under the terms "fight" or "flight." A stimulus sufficiently significant brings about immobility and a high degree of focal awareness of the stimulus. Intense attention is brought to bear on the stimulus and is maintained until the dynamic impassé is resolved by action in avoidance or approach.

The "still reaction" can easily be converted into sleep in laboratory animals, and the situation by which sleep is produced during hypnosis, involving as it does the fixation of a tension, is quite analogous. Similarly, sleep may occur during condition reflex experiments, during periods of delay (Levin, M.: *J. Neurol. & Psychopath.* **16:** 256, 1936), when attention is fixed and the situation is prolonged. The electroencephalographic correlate of the "still reaction" is the attention response characterized by flattening of the brain wave pattern. We have been able to utilize the prolongation of this attention response in the production of sleep hypnotically (Barker, W., and Burgwin, S.: *Psychosom. Med.* **10:** 317, 1948). It is noteworthy that Gibbs observed that convulsive seizures were preceded by a change in brain wave pattern, strongly suggesting the attention response to him. We have noted that the flattening of alpha patterns is the commonest response to significant topics displayed by epileptic patients during interview and that abnormal waves observed are associated with this reaction.

The second fact, noted by Dr. Merritt, is that abnormalities of the brain wave pattern are most likely to appear in light sleep or as drowsing passes into light sleep. It is apparent that the transition between waking and sleep, rather than sleep as such, provides a phase of instability of cerebral function in which abnormal waves most readily appear.

When all these facts are put together, it would appear that the stresses and strains of the patient's life may, when they confront him, acutely bring about a "standstill" of cerebral function, either as a result of their arresting and threatening quality or of his inability to deal further with them for the moment because of their conflictual, irreconcilable nature. At such moments of standstill, the brain may be in a suspended state of function, characterized by the flattening of brain wave patterns. All animals can in such situations easily pass into sleep, and there is no reason to believe that man's brain behaves in any different fashion. Indeed, I have shown that the symptoms of narcolepsy (Barker, W.: *Psychosom. Med.* **10:** 193, 1948) occur in situations of this kind. Gibbs (Gibbs, E. L., and Gibbs, F. A.: *A Research Nerv. & Ment. Dis., Proc.* [1945] **26:** 366, 1947) reported that if seizure wave patterns develop in these light sleep situations and waking stimuli are applied to the patient a seizure may occur. It is clear from our work and Kleitman's (Kleitman, N.: Sleep and Wakefulness, Chicago, University of Chicago Press, 1939) that drowsing or sleeping is a common reaction to adverse life situations. Undoubtedly, in the later life of many persons there are innumerable instances in which the brain is, though briefly, in a state closely resembling light sleep. If a person has, in addition, a mechanism generating the synchronous patterns of the convulsive disorders, convulsive brain wave patterns may be produced at such moments. Hence, when the demands of life apply their demand for waking, one might expect a convulsive reaction.

DR. ERNEST KIRKNER (by invitation): Is there any possibility of prophylaxis? If a patient is suspected early enough in life of having epilepsy, is there any recognized method of prophylaxis?

DR. HAROLD G. WOLFF: Dr. Merritt's interesting suggestion as to the role of acetylcholine in epileptic seizures we have approached in a somewhat different way. Dr. Torda and I have used the synthesis of acetylcholine in a frog's brain, assuming that acetylcholine is produced at a given rate, to test the effect of agents usually employed to make fits either more likely or less likely. Disappointingly, there is no consistency in their effects on the rate of synthesis of acetylcholine in a frog's brain. Some of the agents that increase the tendency to fits increase the amount of acetylcholine, and others decrease it. I do not say this eliminates or weakens Dr. Merritt's thesis, but it is an obstacle to its development.

DR. ALFRED SCHICK: I wish to thank the discussers for their interesting comments. The theme of the evening was a complicated one; and as I was limited for time, according to the rule, the paper may have become too condensed.

One must agree with Dr. Hoch that the unconscious material found in epileptic patients is not specific for the disease. It is similar to that found in neuroses, in psychoses or in the normal person. Why it is expressed in a neurosis in some persons and in a psychosis in others is difficult to determine fully. Furthermore, many factors are involved in the determination of the "choice of a neurosis" and in the choice of an organ system in functional disorders. Environmental and constitutional factors may have an important part in it. The choice of the afflicted region may be determined also by a "somatic compliance," due to the inferiority of an organ system. If one reviews a series of family histories of the present and the past, one often finds a particular item. In one family, one organ system is affected repeatedly, although perhaps in different forms. For instance, one member of the family may have died of cancer of the intestinal tract; another may show polyposis, and in a third neurotic conflicts may express themselves in the gastrointestinal system.

In this paper I wanted to stress that in the precipitation of some seizures emotional factors may be of great importance: not only the emotion, which is obvious and which is caused by obvious external stimuli, but the emotional factor, which is unconscious and which is due to conflicts coming from childhood experiences. I compared this type of seizure—the seizure has to be recognized as a symptom—with an organ neurotic symptom only in the sense that in the latter, too, emotions causing changes in the internal milieu set off a physiopathologic mechanism. According to Fenichel's classification of organ neuroses (Fenichel, O.: *Psychoanalyt. Quart.* **3**: 287, 1945), I mentioned a resemblance of these seizures to what is called "an affect equivalent," that is, the manifestation of a more acute rise or an accumulation of emotional tension by a temporary physical symptom.

As to the question of the frequency of patients like the one I presented, I have not seen many of them, but I have observed in the last five years 4 patients in all of whom there was a great deal of psychologic material, even more striking than in this one. With respect to the effectiveness of psychotherapy, I had the impression that this girl improved, since I could cut down the medication almost to a third of what she received before and still she had less frequent attacks. I had a similar experience with my other patients. The first analyzed case with a good therapeutic result was reported by Stekel (Stekel, W.: Fortschritte der Sexualwissenschaft und Psychoanalyse, *Med. Klin.* **20**: 220 [Feb. 17] 1924).

I do not say that psychotherapy is the treatment for epilepsy; I think the best method at present may be a combination of drug therapy and psychotherapy.

DR. H. HOUSTON MERRITT: I wish to thank the discussers for their stimulating comments. Like Dr. Schick, I made my paper short, not because Dr. McGraw forced me to, but because I did not wish to bore you with statistics and data about various phases of the subject which we know now to be unimportant. For example, the controversy as to whether convulsive seizures were the result of a cortical discharge or of cortical inhibition has been resolved by the work of Berger, in Germany, and of Gibbs, Jasper and others, in this country. The discussers have pointed out that there is no real conflict between investigators who approach this disease from the physiologic side and those who study the psychologic aspects. Admittedly, the seizure is only a symptom, and many things may precipitate this symptom. I should disagree with them that seizures can frequently be precipitated in a healthy, normal person by psychologic stimuli. I

should agree with them that seizures can be precipitated in an epileptic person who has abnormal brain waves and has the basic abnormality on which seizures can easily occur.

Dr. Brenner asked about the relative importance of disorders of the cortex and of the subcortex in the mechanism of the seizure. There is a great deal of discussion in regard to the cortical or subcortical origin of the various types of seizures. Many workers feel that in the petit mal type, which is cited as a classic example of so-called idiopathic epilepsy, the primary discharge is in the subcortical centers, possibly in the thalamus. In the grand mal seizures, particularly in focal seizures, the initial discharge is probably in the cortex. As to some of the other types of seizures, particularly those which are labeled psychomotor, Gibbs is of the opinion that most of those originate in the temporal cortex. The one lesson to be drawn from this session is that the treatment of a patient with seizures should have several aims; he should receive medication to raise the threshold against seizures, and he should be given psychotherapy as protection, so far as possible, from the cruel blows of the environment. Only under experimental conditions should one type of therapy be given. It is poor medical practice to give only chemotherapy or only psychotherapy, and I think it is particularly unwise to give only psychotherapy.